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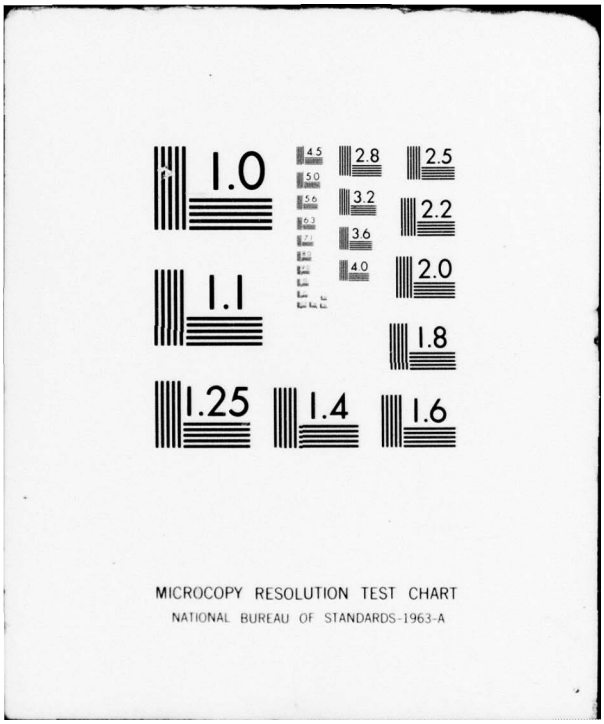
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SYNTHESIS OF BENZOYLBENZOIC ACIDS SUBSTITUTED ANTHRAQUINONES AND RELATED MATERIALS

FINAL REPORT

CHARLES K. BRADSHER, SUBSTITUTE
CHIEF INVESTIGATOR

MARCH 15 1978

U. S. ARMY RESEARCH OFFICE

GRANT NO. DAHC04 74 G0128

DUKE UNIVERSITY

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reagents, organolithium, functionalized
lithiation, selective
cyclizations, base-catalyzed
temperature, low, organic reactions at

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

At -100° a bromine or iodine atom attached to an aromatic nucleus can be replaced rapidly through halogen-metal exchange with butyllithium. Since at this low temperature many functional groups show a surprising unreactivity toward organolithium reagents, it has been found possible to generate many phenyllithium reagents having a functional group at the ortho, meta or para position. Such functional groups have included the chloromethyl, beta

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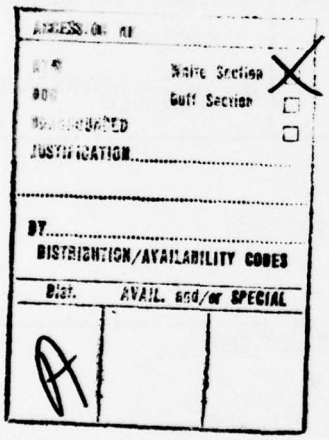
bromoethyl, cyano, carboxylate, carboalkoxy as well as beta carboxyethyl anion and beta carboxamidoethyl groups.

Functionalized phenyllithium reagents have great synthetic utility. Reaction with electrophiles, such a methyl iodide, bromine, benzaphenone, cyclohexonone, phthalic anhydride, benzoate esters, diphenyl disulfide or ethylene oxide replaces the aryl lithium atom resulting in a benzene ring with two functional groups.

Usually, allowing the functionalized aryllithium to warm up results in an interaction between the lithium atom and the functional group. A useful example of such an interaction is the self condensation of lithium ortho-lithio benzoates to yield ortho-benzoylbenzoic acid.

A phenyllithium reagent having a functional substituent in the ortho position are frequently useful intermediates for cyclization.



1. Foreword

In the fall of 1973 the late Prof. William E. Parham submitted to the Army Research Office a research proposal based upon some preliminary results which he had obtained with Duke University funding. As a result of the favorable evaluations of the research proposal, Duke University received a grant of $75,965 for a three-year period May 1, 1974-April 30, 1977, with Dr. Parham as Chief Investigator. Approximately two years after the grant took effect, on May 21, 1976, Dr. Parham's sudden and untimely death deprived us of an esteemed colleague and our country of an outstanding scientist.

After each of Dr. Parham's four graduate students had requested that I assist them in the completion of their theses our departmental chairman, Dr. Louis D. Quin, recommended to the Army Research Office that I be appointed Substitute Chief Investigator for the balance of the grant period. This recommendation was approved.

In the spring of 1977 when it was not clear whether any funding would be available after the expiration of the Parham grant an extension of the expiration date to December 31, 1977, without additional funds was requested and granted.

Fortunately it proved possible to obtain additional funding from the Army Research Office for the grant period 6/15/77 - 6/14/79 under a new grant entitled "Cyclizations Involving Intermediates Obtained by Selective Lithiations". The funds originally awarded for the Parham grant had been exhausted by 6/15/77.

2. List of Appendices (all publications acknowledging support of DAHC04 74 G0128)

1. W. E. Parham and Y. A. Sayed, "Synthesis of Benzoylbenzoic Acids," J. Org. Chem.,39, 2051 (1974).

2. W. E. Parham and Y. A. Sayed, "Synthesis of Isomeric Methyl Benzoylbenzoates and Substituted o, m, and p-Benzoylbenzoic Acids," J. Org. Chem., 39, 2051 (1974).

3. W. E. Parham, L. D. Jones, and Y. Sayed, "Selective Lithiation of Bromoarylalkanoic Acids and Amides at Low Temperature. Preparation of Substituted Arylalkanoic Acids and Indanones," J. Org. Chem., 40, 2394 (1975).

4. W. E. Parham and Y. A. Sayed, "Synthesis of Indenes and 1,2-Dialkylbenzenes," Synthesis, 116 (1976).

5. W. E. Parham, L. D. Jones, and Y. A. Sayed, "Selective Halogen-Lithium Exchange in Bromophenylalkyl Halides," J. Org. Chem., 41, 1184 (1976).

6. W. E. Parham and L. C. Jones, "Elaboration of Bromoaryl-nitriles," J. Org. Chem., 41, 1187 (1976).

7. W. E. Parham and R. M. Piccirilli, "Preparation of Aroylbenzoic Acid. Reaction of Aryllithium Reagents with Phthalic Anhydride," J. Org. Chem., 41, 1268 (1976).

8. W. E. Parham and L. D. Jones, "Halogen-metal Exchange in Esters of Haloaryl Acids," J. Org. Chem., 41, 2704 (1976).

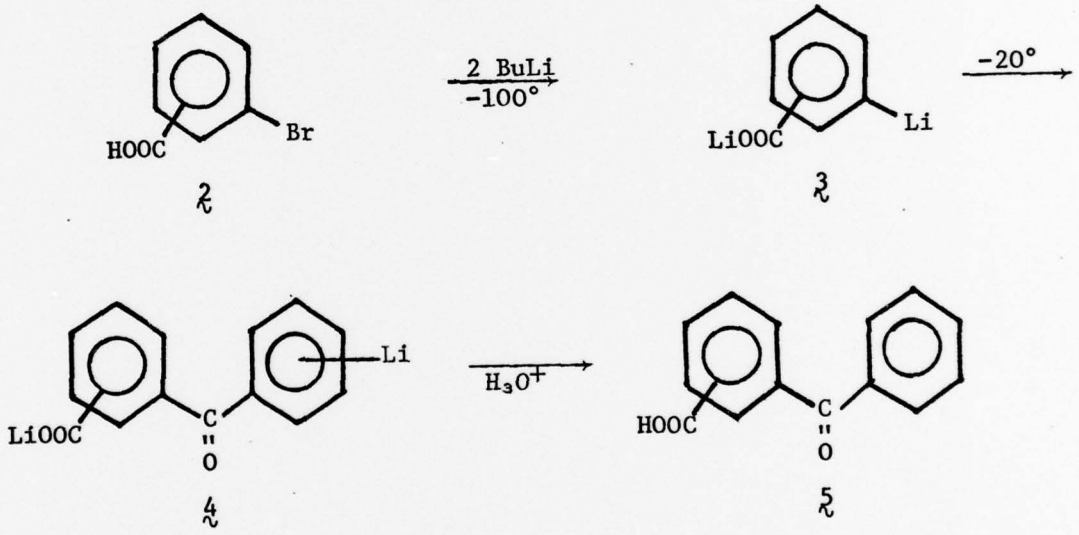
9. W. E. Parham and R. M. Piccirilli, "Selective Halogen-Lithium Exchange in 2,5-Dibromobenzenes and 2,5-Dibromopyridine," J. Org. Chem., 42, 257 (1977).

10. W. E. Parham and D. W. Boykin,"Reactions of Lithioderivatives of Carboxylic Acids. I. 3-Methyl-2-butenoic Acids," J. Org. Chem., 42, 260 (1977).

3. Body of Report

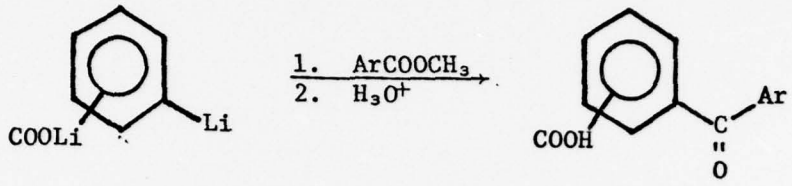
The ten published papers which acknowledge support of the present grant are submitted either as reprints or Xerographic copies and from an essentially complete record of accomplishments during the active life of the grant. In the next few pages an attempt will be made to point out the highlights of what has been accomplished. The reference numbers refer to the appendices (see part 2 of this report).

The synthesis of ortho-benzoylbenzoic acids which was the central theme of the original application was dealt with thoroughly in papers 1, 2 and 7, and 9, although the methods used in the first two papers were also applicable to the more difficult accessible meta and para isomers. If a bromobenzoic acid is subjected to the action of two equivalents of butyllithium at -100° the result is an aryllithium.



reagent 3 bearing a carboxylate anion. This reagent is fairly stable at -100°, but if the temperature is allowed to rise to -20° it undergoes self-condensation affording 4 which on hydrolysis affords the appropriate benzoylbenzoic acid (5) in good yield.[1]

The acylation of the intermediate dianion(3) by the use of methyl esters of benzoic acid derivatives makes possible the preparation of a wide variety of aroyl benzoic acids (6).



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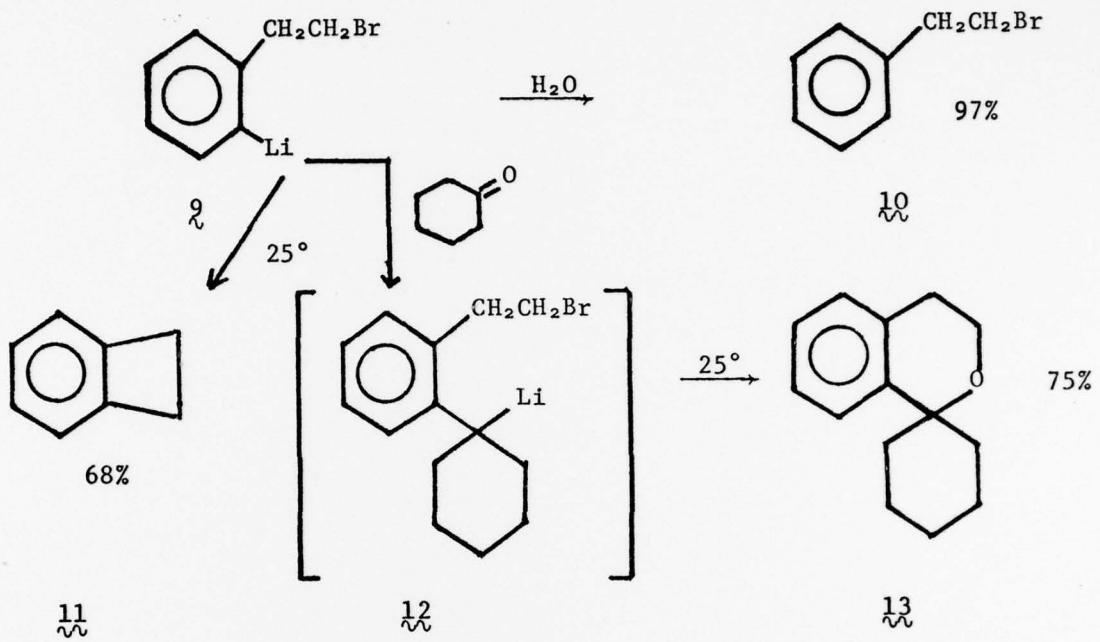
In later work[7] it was shown that the methyl esters could be those of furan 2-carboxylic acid or of 1-methyl indole-2-carboxylic acids.

The first indication of the tremendous synthetic implications of the Parham selective lithiation procedure are to be found in a paper with Jones and Sayed[5] entitled "Selective Halogen-Lithium Exchange in Bromophenylalkyl Halides". It was shown that o-bromobenzyl chloride (7, n=1) or the corresponding bromide 2-(o-bromophenyl)ethyl chloride (7, n=2) or 3-(o-bromophenyl)propyl chloride (7, n=3) of

7 8

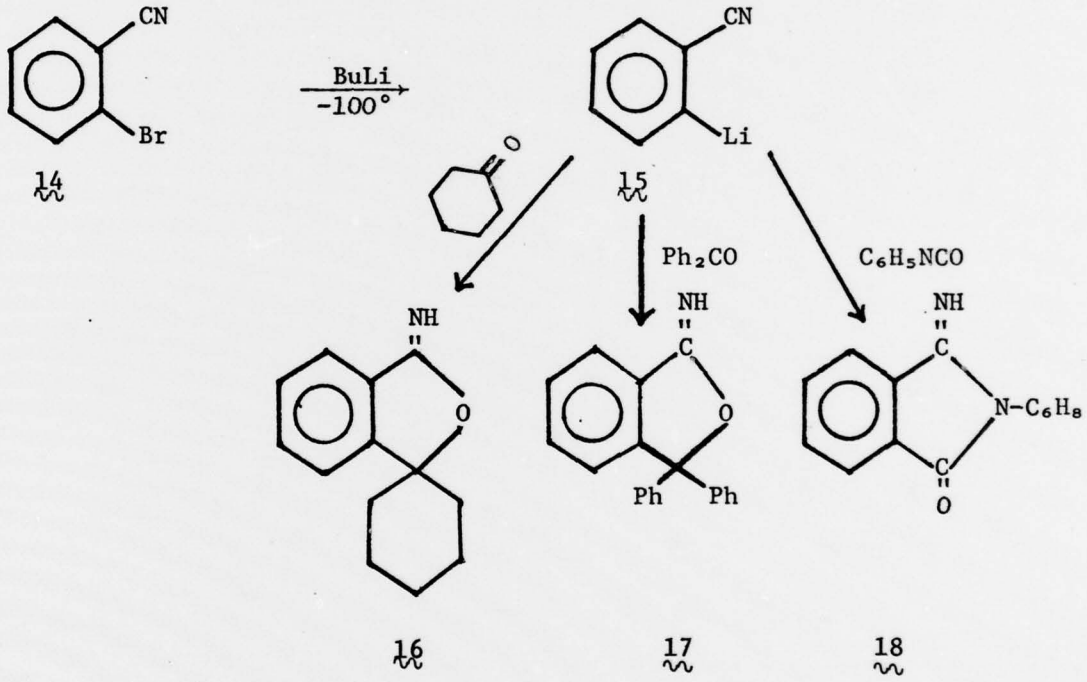
-100° undergo selective halogen exchange at the aryl halogen affording high yields of organolithium reagents (8). An illustration of the usefulness of these reagents in cyclizations is provided by the reactions of 2-(o-bromophenyl)ethyl bromide (9). The quenching of



arylithium reagent 9 with water is a useful way to determine the completeness of the halogen lithium exchange, in this case virtually complete.

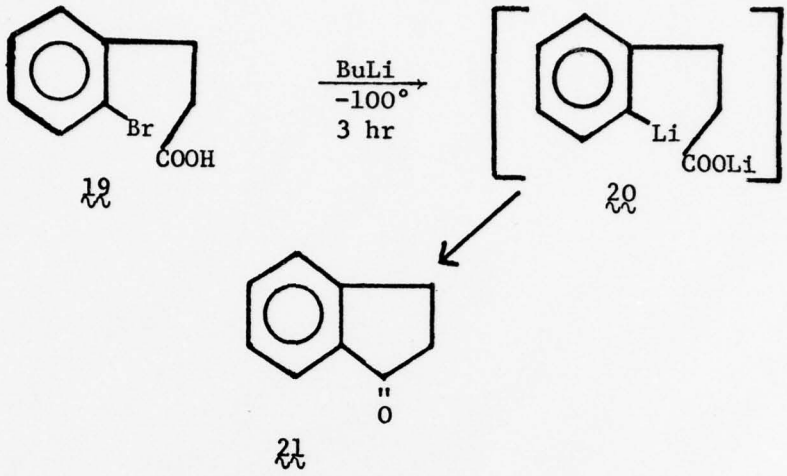
Allowing the organolithium reagent 9 to warm up to room temperature affords the easiest known route to benzocyclobutene (11). The example in which cyclohexanone is the electrophile illustrates an important synthetic strategy which finds repeated application in Parham chemistry. The electrophile adds, creating an anion (in this case 12), which displaces the bromide ion from the side chain forming a heterocyclic system, in this case a spiro isochroman (13).

Some of the same inclination toward cyclization of the primary addition product to form a heterocyclic system may be seen in the reactions of the lithium reagent 15 obtained from o-bromobenzonitrile[6] 14. With cyclohexanone or benzophenone it affords the imines 16 and 17 of phthalides, while with phenylisocyanate the imine derivative of an N-phenylphthalimide (18).



14 15 16 17 18

In an earlier paper[3] Parham, Jones and Sayed showed that 3-(2-bromophenyl)propanoic acid (19) would react with 2.2 equivalents of butyllithium for 45 minutes at -100° to afford the dianion 20 which undergoes cyclization spontaneously affording indanone 21 in



19 20 21

76% yield. The authors pointed out that this new cyclization would offer advantages over the Friedel-Crafts type of ring closure of 3-phenylpropanoic acids in that the lithiation procedure should not be inhibited (as is the Friedel-Crafts procedure) by the presence of electron-withdrawing substituents on the benzene ring.

The work described was carried out with the assistance of the following co-workers:

Post Doctoral Research Associates

Dr. Robert M. Piccirilli 8/74, 12/74

Dr. Yousry Sayed 5/74-5/75, 7/75

Graduate Student Research Assistants:

David W. Boykin	6/76 - 5/77
Kevin J. Edger	2/77
David A. Hunt	9/76 - 5/77
Lawrence D. Jones	9/74 - 2/76
David C. Reames	9/76 - 5/77

4. Bibliography

All bibliographical references in this brief report are to the numbered appendices listed in section 2.

5. Appendices

(Attached)

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Synthesis of Benzoylbenzoic Acids

William E. Parham* and Yousry A. Sayed

Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

Received December 27, 1973

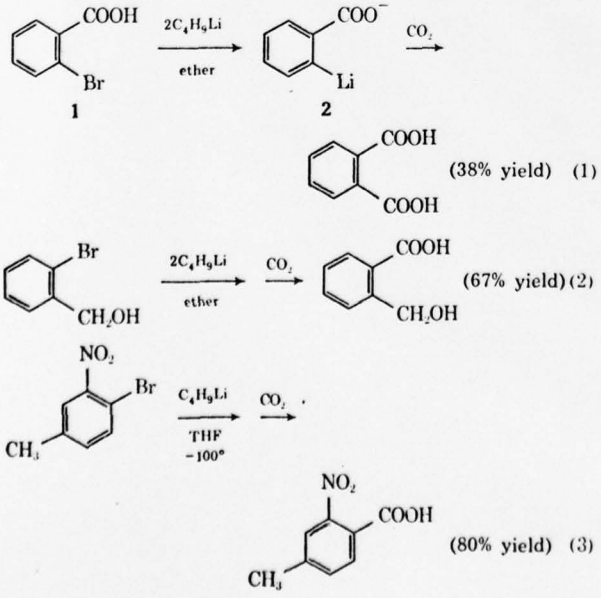
Bromine–lithium exchange in the isomeric bromobenzoic acids with *n*-butyllithium in tetrahydrofuran occurs selectively at −100°. The fate of these ions as a function of temperature has been examined. The dianions are stable at −75° but self-condense readily at −20° to give directly, and in good yield, *o*-, *m*-, and *p*-benzoylbenzoic acid, respectively. Anthraquinone is formed directly from *o*-bromobenzoic acid at higher temperature (0 to −20°).

In his pioneering work in organometallic chemistry, Gilman[1] and his coworkers established that halogen–metal interchange could be achieved with substituted halobenzene derivatives, and that the derived anions could be used as intermediates in synthesis as shown in Scheme I. A variety of halobenzene derivatives were employed in this work containing OH, CN, NH_2, SO_2NH_2, and $SO_2N(C_2H_5)_2$ functional groups; diethyl ether was used as solvent and temperatures of metalation varied from room temperature to −78°. While syntheses from organometallic intermediates of type 1 are potentially quite valuable, the procedure utilizing functionalized aryl halides has largely been overlooked, probably owing to the highly variable yields of benzoic acid derivatives (14–78%) obtained upon carbonation. In 1970, Kobrich and Buck[2] showed that *o*-nitrobromobenzene derivatives could be metalated in high yield (tetrahydrofuran at −100°) (eq 3, Scheme I) while *m*- or *p*-nitrobromobenzene derivatives undergo a redox reaction under these conditions.

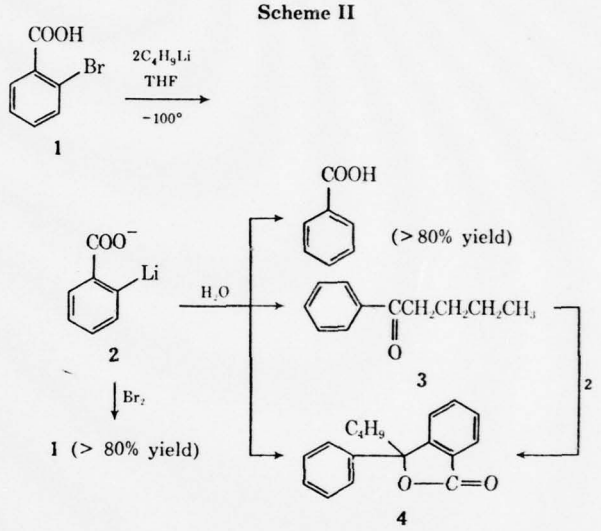
We conclude that bromine–lithium exchange should be highly selective for many substituted halobenzenes at very low temperature (−100°, liquid N_2), and that the variable yields of products previously reported were a consequence of side reactions of derived anions of type 2 with themselves or with solvent. We have, accordingly, reexamined halogen–metal interchange of the isomeric bromobenzoic acids and evaluated the product distribution as a function of temperature.

Reaction of *o*-bromobenzoic acid was studied in detail. When metalation of 1 was conducted at −100° in tetrahydrofuran and the reaction mixture maintained at −75°,

Scheme I



Scheme II



metalation was complete. The product distribution obtained subsequent to quenching the mixture with water is shown in Scheme II.

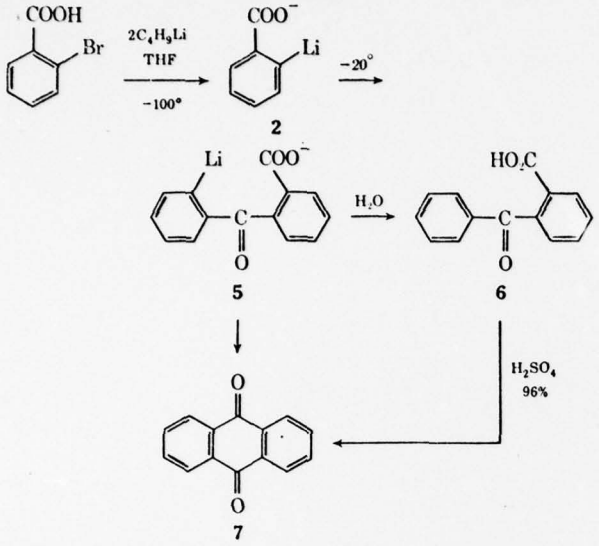
When the anion 2 was added to bromine in carbon tetrachloride, *o*-bromobenzoic acid was formed and isolated in >80% yield. Two minor side products, valerophenone (3, 6%) and lactone 4 (4.5%), were detected in the neutral fraction of the product obtained by addition of 2 to water. Valerophenone was undoubtedly formed by the slow addition of excess butyllithium to the anion 2, and the lactone 4 by addition of 2 to valerophenone. Evidence supporting the latter assumption was obtained by the independent synthesis of 4 (67% yield) by addition of 2 to valerophenone.

The fate of the anion 2 was found to be quite sensitive to temperature (Scheme III). Thus, while the anion 2 is quite stable at −75°, it condenses with itself[3] as the temperature is raised to −20°. Quenching the mixture obtained at −20° with water gave benzoic acid (8.4%), formed from unreacted 2, *o*-benzoylbenzoic acid (6, 63% yield, pure), anthraquinone (7, 2.3% yield) formed by self-condensation of 5, valerophenone (4%), and lactone 4 (7%).

When the temperature of the above reaction mixture was brought to 0°, none of the anion 2 survived nor was there any loss of anion 2 by abstraction of hydrogen from solvent, since no benzoic acid was obtained after addition of water; the yield of anthraquinone rose only slightly to 5.6%, and the yield of *o*-benzoylbenzoic acid was not changed appreciably (64% pure 6).

Attempts to effect a more efficient direct conversion of 5 to 7 were only partly successful, and this is attributed to interaction of 5 with solvent at higher temperature (−20°) to give the salt of 6. Addition of bromine to the solution of

Scheme III



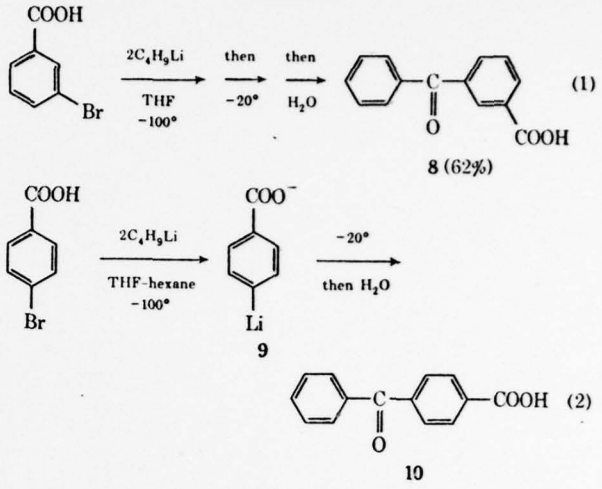
2 prepared at −100° but then warmed up to −20° gave **6** but no detectable amount of bromo acid derived from **5**. Studies with *p*-bromobenzoic acid, discussed subsequently, substantiate loss of anion by reaction with solvent. When the solution of **2**, prepared at −100°, was heated at the reflux temperature (24 hr) prior to addition of water, the yield of anthraquinone was raised to only 15%; the yield of *o*-bromobenzoic acid was reduced to 58%. The stability of anion **2** does appear to be a function of tetrahydrofuran concentration, since the yield of anthraquinone was increased to 44% (26% yield of **6**) when metalation was effected at −100° in a mixture of tetrahydrofuran–hexane (40:60), and the mixture subsequently brought to reflux. Direct formation of anthraquinone (**7**) is of little synthetic consequence, since **7** can be formed[4] essentially quantitatively by reaction of **6** with concentrated sulfuric acid; however, utilization of the derived anion **5** directly for further synthetic transformations does not appear to be feasible.

This efficient one-step synthesis of *o*-benzoylbenzoic acid is of considerable synthetic consequence, since, in view of Gilman's[1] earlier work, it is anticipated that a number of substituted *o*-bromobenzoic acids can be employed which will provide direct access to substituted *o*-benzoylbenzoic acids and, subsequently, to substituted anthraquinones. This is important since the only practical direct synthesis of anthraquinones is the phthalic anhydride synthesis,[5] which is limited by the usual orientation problems and inhibiting action of negatively substitututed benzenes associated with Friedel–Crafts acylation reactions.

The direct formation of benzoylbenzoic acids is by no means limited to *o*-benzoylbenzoic acids. Thus, we have observed (Scheme IV) that *m*-benzoylbenzoic acid (**8**, 62% yield) and *p*-benzoylbenzoic acid (**10**, 55–60% yield) can be obtained directly by obvious modification of the procedure.

The anion **9** was found to be more reactive with solvent tetrahydrofuran than the corresponding anion derived from *o*- and *m*-bromobenzoic acids. Thus, when anion **9**, formed at −100° in tetrahydrofuran at the same concentration used for the preparation of **3** and **8**, was warmed to −20° prior to addition of water the yield of **10** was only 40%; benzoic acid was isolated in 30% yield. When the amount of solvent was increased twofold, only benzoic acid was obtained. Optimum conversion of *p*-bromobenzoic acid to **10** (55–60%) was realized by using a mixture

Scheme IV



of tetrahydrofuran–hexane (60:40); in this case a small amount (5%) of high-melting acid was formed.

Benzoylbenzoic acids of such orientation are not readily prepared by other methods, and it is anticipated that a variety of substituted aroylbenzoic acids can now be conveniently prepared.

Experimental Section

Reaction of *o*-Bromobenzoic Acid with *n*-Butyllithium. A. *n*-Butyllithium (12.5 ml of ~2 *M* solution in hexane, ~0.025 mol) was slowly added (~1 hr) to a solution of **1** (2.5 g, 0.0125 mol) in tetrahydrofuran (50 ml, distilled from $LiAlH_4$). The mixture was maintained under nitrogen and the temperature was controlled by a liquid nitrogen–diethyl ether bath and was not allowed to rise above −95°. The mixture was then allowed to warm to −75° for 2 hr and was then poured into 5% aqueous hydrochloric acid (50 ml). The resulting mixture was extracted with chloroform (100 ml) and the chloroform extracts were washed with water (50 ml). The chloroform solution was extracted with cold 10% aqueous sodium hydroxide (25 ml) to remove acid products, and then washed with water and dried. Acidification of the alkaline extract gave essentially pure benzoic acid (1.25 g, mp 119–120°, 83% yield; 1.21 g after recrystallization from water, 79% yield, mp and mmp 120–122°).

The oil obtained from the chloroform extract was chromatographed on silica gel [preparative tlc, petroleum ether[6]–diethyl ether (80:20) as eluent] to give valerophenone (122 mg, 6%), identified by nmr and infrared, and lactone **4** as an oil; nmr showed butyl group and nine aromatic hydrogens; ir showed five-membered lactone at $\lambda_{C=O}$ 1770 cm^{-1}.

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.97; H, 6.66.

B. When the above reaction mixture was allowed to warm to −20 to −30° and maintained at this temperature for 5 hr prior to quenching, there was obtained (1) benzoic acid (8.4%), (2) *o*-benzoylbenzoic acid [**6**, 68% yield, mp 124–129° by chromatography, silica gel, petroleum ether[6]–ether (80:20) as eluent; 63% from benzene–petroleum ether[6], mp and mmp 128–129° (lit.[7] mp 127°)], along with the ketone **3** (4.2%), the lactone (7%), and anthraquinone (2.3%), mp and mmp 282–285°.

C. When the above mixture was maintained at room temperature for 6 hr prior to addition of water, there was obtained *o*-benzoylbenzoic acid (**6**, 64%), ketone **3** (4%), lactone **4** (8%), and anthraquinone (8.8%).

D. When the above mixture was heated at reflux (24 hr) prior to quenching, the yield of **6** was 55% and the yield of anthraquinone was 15%.

E. The optimum direct conversion of **1** to anthraquinone (44%) was obtained in experiments similar to D but by using tetrahydrofuran–hexane (40:60) as solvent; the yield of **6** was reduced to 26%.

Preparation of Lactone 4. Valerophenone (0.81 g, 0.005 mol) was added at −75° to a solution of **2** (~0.005 mol) as prepared in A above. The mixture was allowed to warm to room temperature. The lactone **4** was converted to the salt in warm aqueous base which was reconverted to lactone on acidification, yield of **4** 67%.

Conversion of 2 to *o*-Bromobenzoic Acid. A solution of **2** was prepared as described in A and prior to quenching was added to bromine (excess in carbon tetrachloride). The acid **1** was isolated by conventional means and obtained in nearly quantitative yield.

***m*-Benzoylbenzoic acid** was prepared from *m*-bromobenzoic acid (0.0125 mol) by a procedure essentially identical with that described in B; the mixture was maintained at −20 to −10° (5 hr) prior to quenching with water. There was obtained (1) benzoic acid (mp 118–120°, 9.2%), (2) *m*-benzoylbenzoic acid [**8**, 69%, mp 155–158°; 63% from chloroform–petroleum ether,[6] mp and mmp 161–162° (lit.[8] mp 161–162°)]. The neutral fraction contained only trace quantities of products other than valerophenone (9%).

***p*-Benzoylbenzoic acid** was prepared from *p*-bromobenzoic acid as described for **8**. The acid fraction on chromatography [silica gel, petroleum ether[6]–diethyl ether (70:30) as eluent] gave *p*-benzoylbenzoic acid [40%, mp 199–201° (lit.[9] mp 197–200°)] and benzoic acid (30%).

When the amount of tetrahydrofuran was increased twofold, only benzoic acid was obtained.

When the procedure was carried out as described for **8** but with a mixture of tetrahydrofuran–hexane (60:40) the yield of *p*-benzoylbenzoic acid was 55–60% (multiple runs).

Acknowledgment. The authors would like to express their appreciation to the U. S. Army Research Office through Grant DAHCO4 74 GD128 for partial support of this work.

Registry No.—**1**, 88-65-3; **2**, 51310-60-2; **4**, 51310-61-3; **6**, 85-52-9; **8**, 579-18-0; **10**, 611-95-0; *n*-butyllithium, 109-72-8; benzoic acid, 65-85-0; *m*-bromobenzoic acid, 585-76-2; *p*-bromobenzoic acid, 586-76-5.

References and Notes

(1) (a) H. Gilman and C. Arntzen, *J. Amer. Chem. Soc.*, **70**, 4178 (1948); (b) *ibid.*, **70**, 2844 (1948); (c) H. Gilman and D. S. Melstrom, *ibid.*, **63**, 2844 (1941).
(2) G. Kobrich and P. Buck, *Chem. Ber.*, **103**, 1412 (1970).
(3) The possibility that **6** was formed by a sequence involving reaction of **2** with *n*-butyl bromide to form an ester with subsequent condensation of the derived ester with **2** was not supported by the observation that the lithium salt of benzoic acid does not react with *n*-butyl bromide at −20°.
(4) (a) A. H. Gleason and G. Dougherty, *J. Amer. Chem. Soc.*, **51**, 310 (1929); (b) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath, Boston, Mass., 1957, p 159.
(5) *Cf.* E. Barnett, "Anthracene and Anthraquinones," Bailliere, Tindall and Cox, London, 1921.
(6) Boiling point 30–60°.
(7) C. R. Rubidge and N. C. Qua, *J. Amer. Chem. Soc.*, **36**, 732 (1914).
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Synthesis of Isomeric Methyl Benzoylbenzoates and Substituted *o*-, *m*-, and *p*-Benzoylbenzoic Acids

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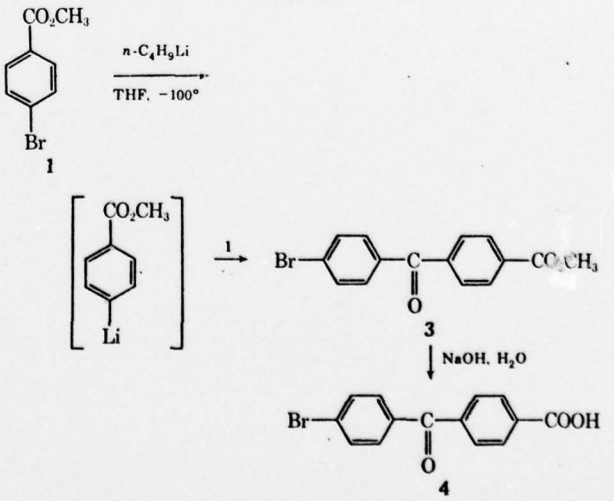
Received December 27, 1973

n-Butyllithium reacts selectively at −100° with isomeric methyl bromobenzoates by halogen–metal exchange. The corresponding anions derived from the meta and para isomers react readily with methyl ester functions at −100°; however, the anion derived from the ortho isomer reacts only slowly at this temperature, which permits complete metal–halogen interchange. The self-condensation of isomeric methyl bromobenzoates, and the reactions of dianions derived from the isomeric bromobenzoic acids with substituted methyl benzoates, provide ready access to a wide variety of *o*-, *m*-, and *p*-benzoylbenzoic acids.

In a previous communication[1] we reported a convenient procedure for a one-step conversion of bromobenzoic acids to *o*-, *m*-, and *p*-benzoylbenzoic acids. While it is apparent that this concept can be extended to a variety of substituted halobenzene derivatives, we were particularly interested in examining comparable reactions of the isomeric methyl bromobenzoates with *n*-butyllithium; it was anticipated that an understanding of competitive halogen–metal exchange *vs.* carbonyl addition reactions in such systems would permit a more versatile procedure for the preparation of a variety of isomeric aroylbenzoic acids.

A. Self-Condensation of Methyl Bromobenzoates. Methyl esters are considerably more reactive to anion addition reactions than carboxylate ions previously studied;[1] nevertheless, reaction of methyl *p*-bromobenzoate with *n*-butyllithium in tetrahydrofuran at −100° is selective in that the primary reaction involves halogen–metal interchange rather than addition of alkyllithium to the carbonyl ester function. The derived anion **2** did, however, react as formed at the ester function of unreacted **1**, as shown in Scheme I.

Scheme I



The principal product, methyl 4-(*p*-bromobenzoyl)benzoate (**3**), obtained pure in 63% yield when 0.75 molar equiv of *n*-butyllithium was employed, was unknown, and was further characterized by hydrolysis (~100% yield) to the corresponding acid **4**. The yield of **3** was optimum with approximately 0.75 molar equiv of *n*-butyllithium. The yield of **3** dropped to 49% when 0.6 molar equiv of *n*-butyllithium was employed, and in this case 9% of **1** was recovered unchanged; when 1 molar equiv of *n*-butyllithium was employed the yield of **3** was 57%.

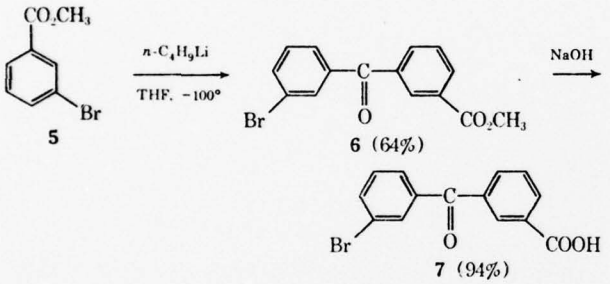
The temperature of the above reaction was found to be critical if high yields of bromo ester **3** are to be obtained.

When **1** was treated with *n*-butyllithium at −75° the yield of **3** was only 10–15%. The principal product in this case was a neutral oil which contained OH, n-C_4H_9, and CO_2CH_3 functions (by ir and nmr), establishing competitive reactions of *n*-butyllithium with ester or carbonyl functions; however, this material gave an oily acid on hydrolysis and was not examined further.

The above sequence provides a remarkably easy route to methyl 4-(*p*-bromobenzoyl)benzoate (**3**) and it is assumed that the method can be extended to related compounds containing substituents less reactive to anion addition than the ester function.

The sequence is by no means limited to the synthesis of benzoic acids substituted in the para position. Thus, when methyl *m*-bromobenzoate was treated similarly with 0.75 molar equiv of *n*-butyllithium at −100°, no unchanged bromo ester **5** was detected and methyl 3-(*m*-bromobenzoyl)benzoate (**6**) (Scheme II) was obtained directly in 64% yield (pure). The ester **6** was unknown and was further characterized by conversion to the new acid **7**.

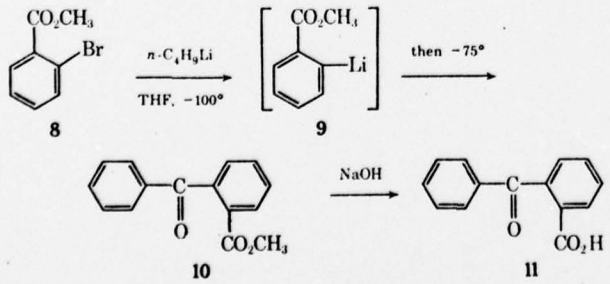
Scheme II



5 **6** (64%) **7** (94%)

The reaction of methyl *O*-bromobenzoate (**8**) with *n*-butyllithium followed a different course than that observed for the meta and para isomer, although, as for reactions of **1** and **5**, metal–halogen interchange occurred rather than direct addition of alkyllithium to the ester function (Scheme III). Reaction of the intermediate anion **9** with unchanged bromo ester **8** was slow at −100°, as anticipated from steric considerations, which permitted complete metalation of **8** to **9**. When the mixture was warmed to −75° the anion **9** self condensed and, subsequent to addition of water, there was obtained an 88% yield of methyl *o*-benzoylbenzoate (**10**). Although we could not induce this low-melting ester to crystallize, it was pure by nmr, and was hydrolyzed in essentially quantitative yield to *o*-benzoylbenzoic acid (**11**).

Scheme III

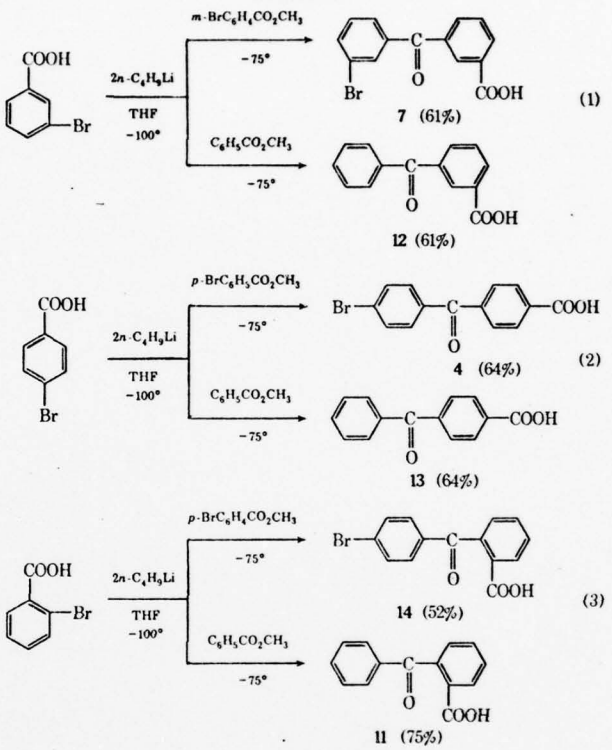


8 **9** **10** **11**

In the above experiment it was found expedient to use 1 molar equiv of *n*-butyllithium; use of 0.75 molar equiv of *n*-butyllithium gave **10** in 49% yield and appreciable starting ester **8** (31%).

B. Crossover Experiments. In view of the stability of the dianions prepared from the isomeric bromobenzoic acids[1] at −100° and the reactivity of the methyl ester group toward aryl anions observed at −100 to −75°, it became apparent that a seemingly broad spectrum of substituted benzoic acids could be prepared by crossover experiments. While we have not yet defined the scope of this method, we have demonstrated its utility by the examples outlined in Scheme IV.

Scheme IV

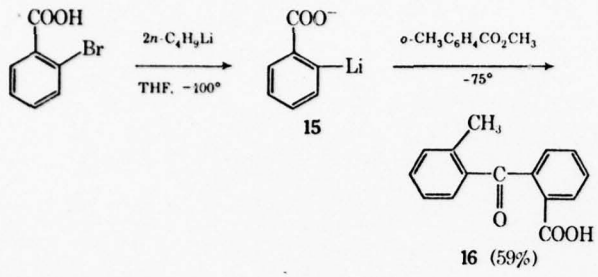


Since the only obvious limitation to this synthesis of isomeric aroylbenzoic acids is that the ester moiety contain functional groups less reactive toward nucleophilic addition than the ester function itself, it is apparent that this scheme constitutes a useful method, based on Gilman's pioneering work, for the synthesis of aromatic compounds. In view of the limited scope of the only other practical synthesis of anthraquinones (from *o*-benzoylbenzoic acids prepared by the Friedel–Crafts phthalic anhydride synthesis[2]) this procedure should prove of value for the preparation of precursors to anthraquinones and polynuclear aromatic systems not easily available by other routes.

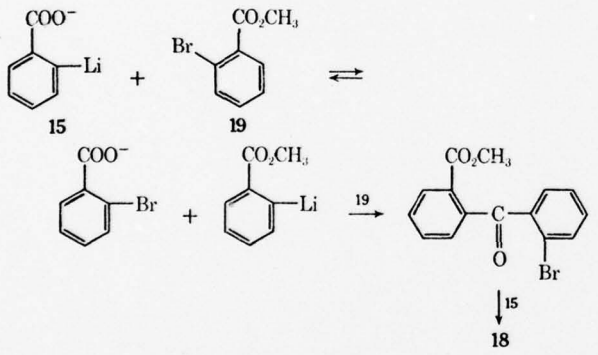
The procedure is also applicable for the preparation of the more hindered ortho,ortho-substituted cases summarized in Scheme V. Thus, reaction of **15** with methyl *o*-toluate gave **16** (59%, pure). Reaction of **15** with methyl *o*-bromobenzoate was of interest since in addition to the expected acid **17** (45%), there was also obtained an appreciable quantity (29%) of trimer acid **18**. While **18** could theoretically form by addition of **15** to the salt of **17**, this seems unlikely, since in no other case have we observed such addition to carboxylate functions at −75°. It seems more likely that **18** is formed by competitive lithium exchange reactions as, for example, shown in Scheme VI; however, this possibility has not been examined.

It would appear that the condensation of dianions of type **15** with acid halides is not as efficient for the preparation of *o*-benzoylbenzoic acids as is condensation with the corresponding ester. Formation of considerable amounts of **23** (19%) along with **16** (41%) by addition of **20**

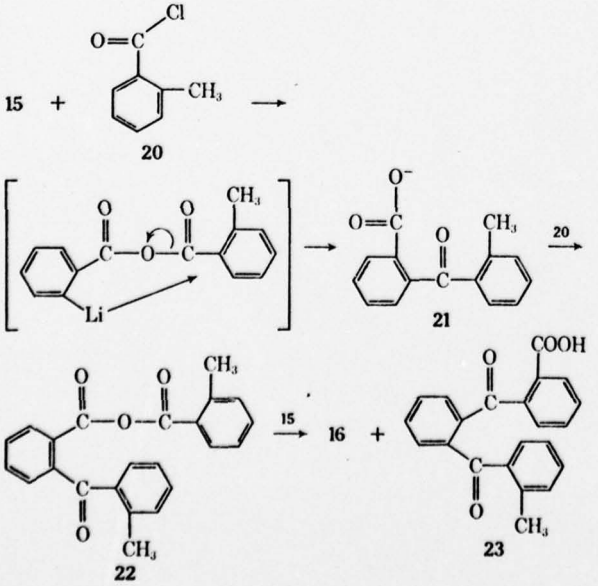
Scheme V



Scheme VI



Scheme VII



to **15** at −75° is consistent with the conclusion that anhydride formation is faster (or competitive) with carbanion addition as summarized in Scheme VII. Similarily, addition of *o*-bromobenzoyl chloride to **15** at −75° gave a mixture of **17** (31%) and **18** (29%).

Experimental Section

Self-Condensation of Methyl Bromobenzoates. Reaction of Methyl *p*-Bromobenzoate (1) with *n*-Butyllithium. *n*-Butyllithium (9.4 ml of ~2 *M* solution in hexane, ~0.0185 mol) was slowly added (1 hr) to a solution of **1** (5.4 g, 0.025 mol, predried) in tetrahydrofuran (50 ml, distilled from $LiAlH_4$). The mixture was under nitrogen and the temperature was not allowed to rise above −95° (liquid N_2, diethyl ether). The mixture was allowed to warm to −75° and after 3 hr was poured into 5% aqueous hydrochloric acid (50 ml). The resulting mixture was extracted with ether and the extracts were dried ($MgSO_4$). The white solid (5.2 g, mp 110–130°) obtained by removal of ether was recrystallized from chloroform–methanol to give 2.5 g of methyl 4-(*p*-bromobenzoyl)benzoate (**3**, 63% yield, mp 177–178°).

Anal. Calcd for $C_{15}H_{11}BrO_3$: C, 56.45; H, 3.47; Br, 25.04. Found: C, 56.66; H, 3.63; Br, 24.95.

When 0.6 molar equiv of *n*-butyllithium was used, the yield of **3** was 49%; 9% of **1** was recovered; with 1 molar equiv of *n*-butyllithium the yield of **3** was 57%.

4-(*p*-Bromobenzoyl)benzoic acid (**4**, 96% yield, mp 274° from chloroform–methanol) was obtained from **3** by alkaline hydrolysis.

Anal. Calcd for $C_{14}H_9BrO_3$: C, 55.10; H, 2.97; Br, 26.19. Found: C, 54.77; H, 3.28; Br, 26.29.

Methyl 3-(*m*-bromobenzoyl)benzoate (**6**, 64% yield, mp 98–99° from methanol) was obtained from methyl *m*-bromobenzoate (**5**) as described above for **3**.

Anal. Calcd for $C_{15}H_{11}BrO_3$: C, 56.45; H, 3.47; Br, 25.04. Found: C, 56.22; H, 3.67; Br, 25.21.

3-(*m*-Bromobenzoyl)benzoic acid (**7**, 94% yield, mp 231–232° from chloroform–methanol) was obtained from **6** by alkaline hydrolysis.

Anal. Calcd for $C_{14}H_{19}BrO_3$: C, 55.10; H, 2.97; Br, 26.19. Found: C, 54.93; H, 3.07; Br, 26.34.

Methyl *o*-Benzoylbenzoate (10). Reaction of methyl *o*-bromobenzoate with *n*-butyllithium (0.75–1.0 molar equiv) was carried out as described above for **3** to give a yellow oil which showed one major and two minor components by tlc [silica gel, petroleum ether[3]–diethyl ether (80:20)]. The product was chromatographed on silica gel to give 0.264 g (88% yield) of **10** as a light yellow oil (lit.[4] mp 52°) which showed no impurities by nmr. Hydrolysis of the ester with aqueous sodium hydroxide gave quantitative conversion to *o*-benzoylbenzoic acid (mp and mmp[5] 128–129°).

Crossover Experiments. 3-(*m*-Bromobenzoyl)benzoic Acid (7). In a typical experiment *m*-bromobenzoic acid (2.5 g, 0.0125 mol) was converted to the corresponding dianion with *n*-butyllithium (0.25 mol) as previously described.[1] The temperature was allowed to warm to −75° for 2 hr and a solution of methyl *m*-bromobenzoate (2.7 g, 0.0125 mol) in dry tetrahydrofuran (10 ml) was added sufficiently slowly to maintain the mixture at −75 to −70°. The resulting mixture was stirred for 2 hr at −75° then allowed to warm to −20° and poured into 5% aqueous hydrochloric acid (100 ml); the resulting mixture was extracted with ether (400 ml total) which was in turn washed with water (50 ml). Acidic products were removed from the ether extract by extraction with 10% aqueous sodium hydroxide (50 ml) and the acids were regenerated (dilute hydrochloric acid) and collected by filtration. The crude acids (3.5 g, mp 205–220°) was recrystallized from chloroform–methanol to give 3-(*m*-bromobenzoyl)benzoic acid (61% yield, mp and mmp 232°).

***m*-Benzoylbenzoic acid** [**12**, 61% pure, mp and mmp 161–162° by chromatography (preparative tlc, silica gel using petroleum ether[3] as eluent, lit.[6] mp 161–162°)] was obtained from *m*-bromobenzoic acid and methyl benzoate.

4-(*p*-Bromobenzoyl)benzoic acid (**4**, 64% yield, mp and mmp of product obtained from methyl *p*-bromobenzoate was 274°) was obtained from *p*-bromobenzoic acid and methyl *p*-bromobenzoate.

***p*-Benzoylbenzoic acid** [**13**, 64% yield, mp 198–201°, by chromatography on silica gel, petroleum ether[3]–diethyl ether (80:20) as eluent, lit.[7] mp 197–200°] was prepared from *p*-bromobenzoic acid and methyl benzoate.

2-(*p*-Bromobenzoyl)benzoic acid (**14**, 52% yield, mp 170–172° from chloroform–petroleum ether,[3] lit.[8] mp 172–173°) was prepared from *o*-bromobenzoic acid and methyl *p*-bromobenzoate.

o-**Benzoylbenzoic acid** (75% yield, mp 127–129° from benzene–petroleum ether,[3] lit.[5] mp 128–129°) was prepared from *o*-bromobenzoic acid and methyl benzoate.

2-(*o*-Methylbenzoyl)benzoic Acid (16) and the Acid 23. A. The acidic product obtained as described for **7** by reaction of methyl *o*-toluate with the dianion prepared from *o*-bromobenzoic acid was chromatographed on silica gel [preparative tlc, petroleum ether[3]–diethyl ether (70:30) as eluent] to give 2-(*o*-methylbenzoyl)benzoic acid (**16**), 59% yield, mp 107–109°[9] from benzene–petroleum ether.[3] No appreciable amount of **23** was isolated.

Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03; neut equiv, 240.02. Found: C, 75.03; H, 5.25; neut equiv, 238.

B. When *o*-toluoyl chloride was used instead of methyl *o*-toluate and the acidic product was chromatographed as in A the yield of **16** was 41% and the acid **23** was obtained in 19% yield, mp 240–242° from ethanol–water.

Anal. Calcd for $C_{22}H_{16}O_4$: C, 76.73; H, 4.68; neut equiv, 344.3. Found: C, 76.58; H, 4.89; neut equiv, 345.

2-(*o*-Bromobenzoyl)benzoic Acid (17) and the Acid 18. A. The acidic product obtained as described for **7** by reaction of methyl *o*-bromobenzoate (2.77 g, 0.125 mol) with the dianion prepared from *o*-bromobenzoic acid was recrystallized from methanol–chloroform to give **18** as a white solid, 29% yield, mp 284–286°.

Anal. Calcd for $C_{21}H_{13}BrO_4$: C, 61.63; H, 13.20; Br, 19.45; neut equiv, 409.2. Found: C, 61.43; H, 3.67; Br, 19.16; neut equiv 408.

The mother liquor obtained above was chromatographed on silica gel [preparative tlc, petroleum ether[3]–diethyl ether (60:40) as eluent] to give 2-(*o*-bromobenzoyl)benzoic acid (**17**), 45%, mp 134° from chloroform–petroleum ether.[3]

Anal. Calcd for $C_{14}H_9BrO_3$: C, 55.10; H, 2.97; Br, 26.19; neut equiv, 305.1. Found C, 54.89; H, 2.91; Br, 26.00; neut equiv, 304.

B. When *o*-bromobenzoyl chloride was used instead of methyl *o*-bromobenzoate, the yield of **18** was 27–30% and the yield of **17** was 40–44% (multiple runs including addition of the dianion at −75° to the acid chloride solution in hexane at room temperature, *i.e.*, reversed addition).

Acknowledgment. The authors would like to express their appreciation to the U. S. Army Research Office through Grant DAHCO4 74 GD128 for partial support of this work.

Registry No.—**1**, 619-42-1; **3**, 51310-29-3; **4**, 51310-30-6; **5**, 618-89-3; **6**, 51310-31-7; **7**, 51310-32-8; **10**, 606-28-0; **16**, 5469-51-2; **17**, 51310-33-9; **18**, 5130-34-0; **23**, 51310-35-1; *n*-butyllithium, 109-72-8; methyl *o*-bromobenzoate, 610-94-6; *m*-bromobenzoic acid, 585-76-2; methyl benzoate, 93-58-3; *p*-bromobenzoic acid, 586-76-5; *o*-bromobenzoic acid, 88-65-3; methyl *o*-toluate, 118-90-1; *o*-toluoyl chloride, 933-88-0; *o*-bromobenzoyl chloride, 7154-66-7.

References and Notes

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(3) Boiling point 30–60°.
(4) I. M. Heilbron, "Dictionary of Organic Compounds," Vol. 1, 4th ed, Oxford University Press, London, 1953, p 357.
(5) C. R. Rubidge and N. C. Qua, *J. Amer. Chem. Soc.*, **36**, 732, (1914).
(6) S. Senff, *Justus Liebigs Ann. Chem.*, **220**, 252 (1883).
(7) E. Wertheim, *J. Amer. Chem. Soc.*, **55**, 2541 (1933).
(8) C. F. H. Allen and J. W. Gates, Jr., *J. Amer. Chem. Soc.*, **65**, 422 (1943).
(9) M. S. Newman and C. D. McCleary, *J. Amer. Chem. Soc.*, **63**, 1537 (1941), reported a melting point of 130–132° after standing for several months; however, the initial melting point of the acid was 113.8–115°.

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Selective Lithiation of Bromoarylalkanoic Acids and Amides at Low Temperature. Preparation of Substituted Arylalkanoic Acids and Indanones[1]

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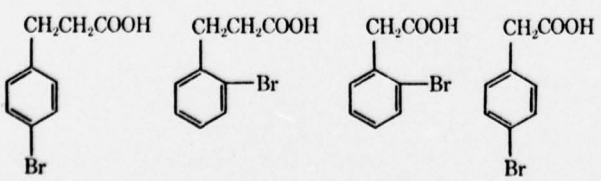
Received December 5, 1974

Studies of *p*-bromophenylpropanoic acid suggest that *p*-, and presumably *m*-, bromoarylalkanoic acids can be conveniently elaborated by selective halogen–metal exchange with *n*-butyllithium at −100° followed by reaction with E^+. Metal–halogen exchange is also selective for ortho-substituted acids; however, *o*-bromoarylpropanoic acids lead directly to indanones in high yield. Amide anions have been shown to be less reactive toward organolithium derivatives than carboxylate; consequently, by masking the carboxylic acid group by conversion to the amide anion, indanone formation can be obviated and elaboration of *o*-bromophenylpropanoic acid can be achieved. *o*-Bromophenylacetic acid (3) reacts with *n*-butyllithium at −100 or at −78° to give the dilithio derivative **21** and the trilithio derivative **23**. The trilithio derivative undergoes anion decay, with time, by reaction with solvent, to give **21**; consequently, by control of conditions, products can be obtained selectively from either **21** or **23**. Similar results were obtained with *p*-bromophenylacetic acid (4); however, in contrast to the results obtained with **3**, alkylation of intermediate anions with *n*-butyl bromide, formed during metal interchange, occurs which detracts from synthetic applications in the latter case.

Although Grignard (or lithium) reagents of aryl halides are useful intermediates for formation of aryl–carbon bonds, utilization of such derivatives has been of limited value for aromatic nuclei containing sensitive electron-withdrawing groups. Meyers and Temple[2] have obviated problems associated with aromatic carboxylic acids by disguising the carboxylic function as the corresponding oxazoline derivative. Recently we have shown[3a,b] that the lithium salt of aryl carboxylic acid function provides adequate protection of the carboxylic acid group at −100° to lithium reagents, and that high yields of elaborated arylcarboxylic acids can be obtained directly from *o*-, *m*-, and *p*-bromobenzoic acids.

We have now examined the reaction of acids 1–4 with *n*-butyllithium at −100° as part of a program designed to test

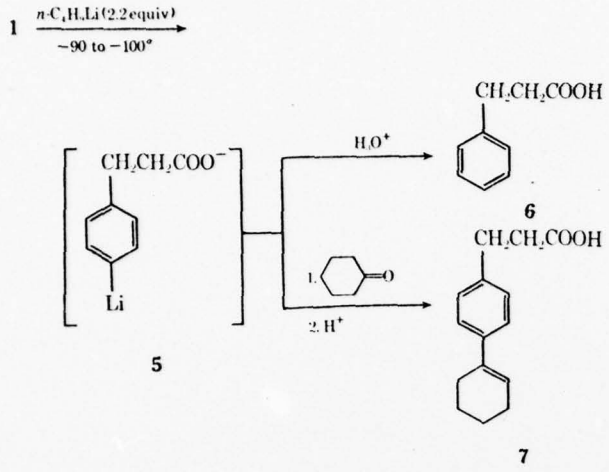


1 **2** **3** **4**

the generality of the above method for the elaboration of alkanoic acids. Acid **1** was selected as a model for the behavior expected for a broad series of para- and meta-substituted bromoarylalkanoic acids. Limitations for utilization of bromoarylalkanoic acids were anticipated where favorable entropy relationships might result in intramolecular reaction of derived aryllithium reagents with carboxylate functions (as in **2**), and in phenylacetic acids (**3** and **4**) where the methylene group α to the carboxylate function is more acidic. In all cases, progress of metal–halogen exchange was followed by quenching aliquots[4] with dilute acid and determining the ratio (by NMR) of recovered bromo acid to acid derived by replacing bromine with hydrogen.

A. β-(*p*-Bromophenyl)propanoic Acid (1). Two equivalents of *n*-butyllithium was added rapidly to a solution of **1** in THF–hexane at −100° at such a rate that the temperature did not exceed −90°. Examination of an aliquot showed that halogen–lithium exchange was ~80% after 30 min and the ratio did not change appreciably after an additional 90 min at −100°. Additional *n*-butyllithium (up to 0.4 to 1 equiv) increased the degree of exchange only slightly (ratio of 1:6 was ~85%); however, with excess *n*-butyllithium and time, small quantities of butylated products were detected (NMR) in the neutral component of the aliquots. In subsequent experiments 2.2 equiv of *n*-butyllithium was employed and the mixture was stirred at −100° for 45 min prior to quenching. In one experiment (see Scheme I) the mixture was quenched with water; the yield

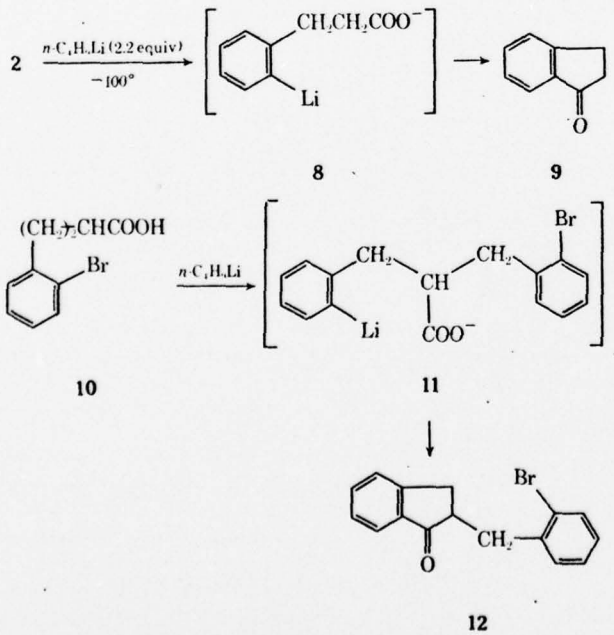
Scheme I



of **6**, isolated pure by distillation, was 86%. The residual acidic product was a mixture of **1**, **6**, and a trace of butylated acid.[5] In another experiment **5** was quenched with cyclohexanone;[6] the yield of nearly pure **7** was 67% (59% pure). In no case was there any evidence that **5** self-condensed at −100°. It was concluded, therefore, that, except for the limitations described in B and C (below), the procedure described should prove to be a useful one for the elaboration of *m*- and *p*-arylalkanoic acids.

B. β-(*o*-Bromophenyl)propanoic Acid (2). This acid was chosen for study since it was anticipated that favorable entropy considerations may lead to self-condensation of **8**, leading to indanone (**9**).

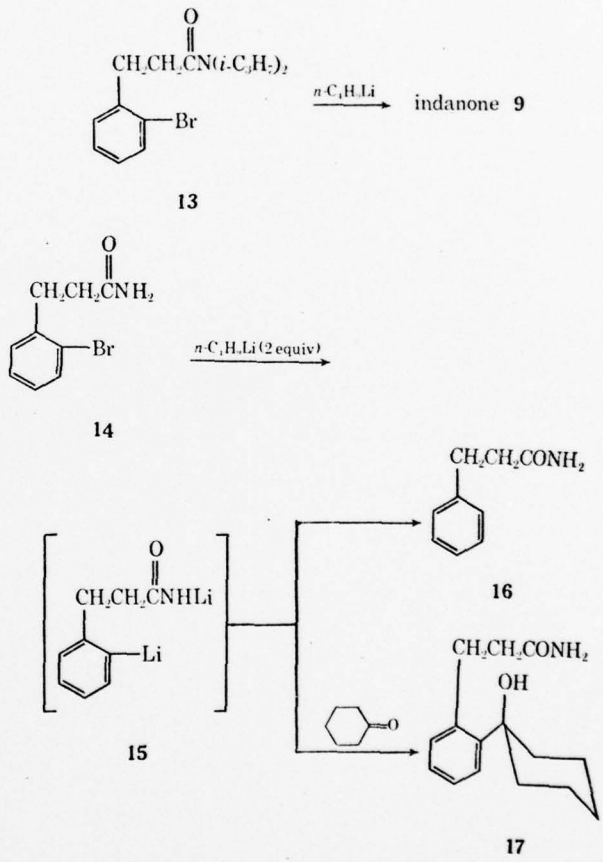
Scheme II



Reaction of **2** with *n*-butyllithium was indeed selective at −100° in that halogen–metal exchange occurred without proton abstraction from the methylene group or without addition of *n*-butyllithium to carboxylate; however, as anticipated, cyclization occurred at −100° to give indanone. Studies of aliquots[4] showed that cyclization was appreciable after 60 min at −100°. The mixture was stirred at −100° for 3 hr; the yield of indanone,[6] isolated pure by distillation, was 76%. While this observation defines a limitation to the general elaboration of bromoarylalkanoic acids suggested in A (above), this new synthesis should be of value for the preparation of indanones not easily available by more conventional routes.[7] In a similar experiment, reaction of **10** (Scheme II) with 2 equiv of *n*-butyllithium afforded a good yield of **12** (66%). Significantly, reaction of **10** with 3 equiv of *n*-butyllithium leads to 2-benzylindanone (72% yield).[8]

Amide ions were found to be less reactive than carboxylate ions toward organolithium reagents; consequently, cyclization of *o*-bromoarylpropanoic acids to indanones can be obviated by utilizing certain amides derived from the acid (Scheme III). Reaction of the dialkylamide **13** with 1

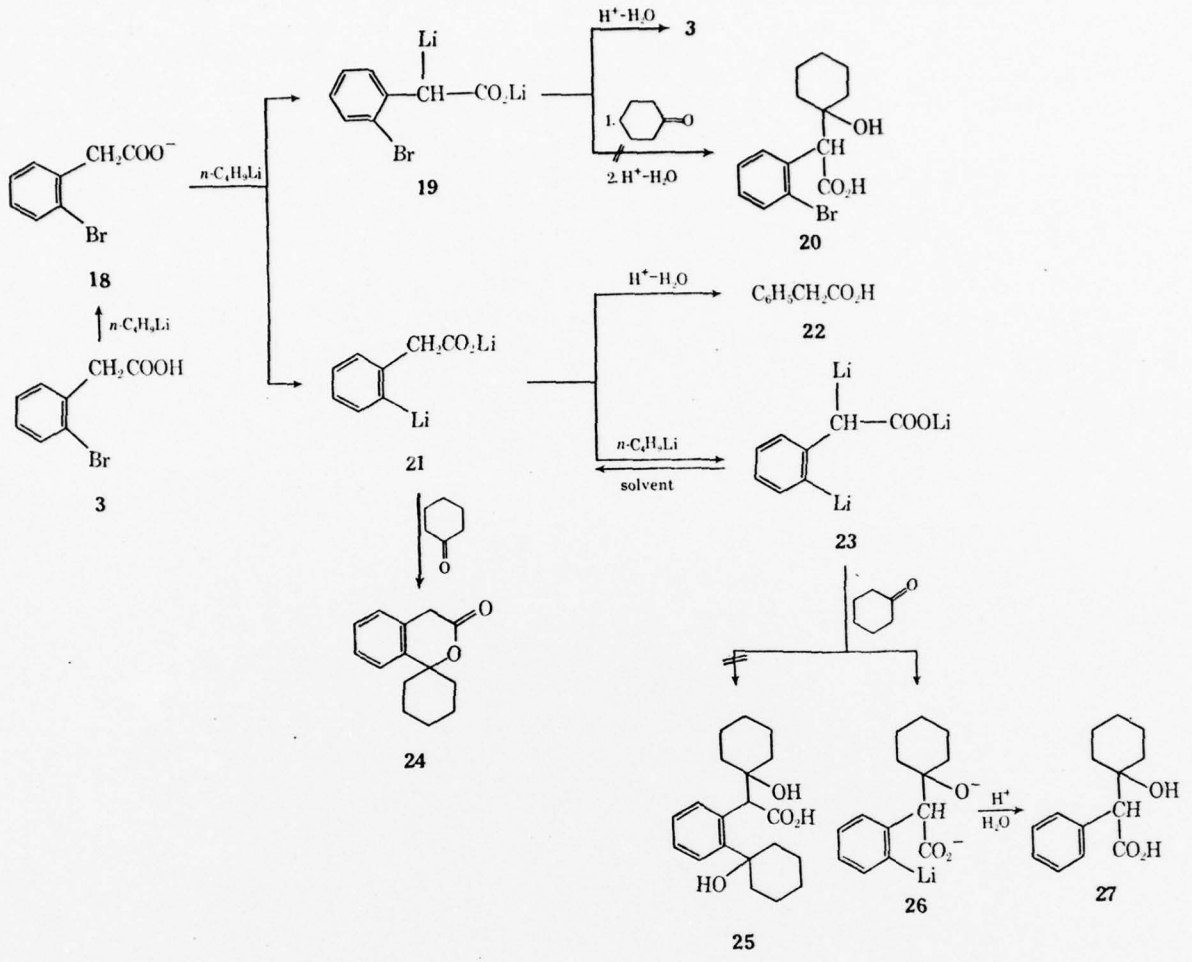
Scheme III



equiv of *n*-butyllithium at −100° leads directly to indanone (61% yield by isolation). By contrast, reaction of the unsubstituted amide **14** with 2 equiv of *n*-butyllithium leads to the dilithio derivative **15**, which does not cyclize at −100°. Reaction with acid gave **16** in 81% yield (isolated); amide **17** was isolated pure in 40% yield when **15** was quenched with cyclohexanone. Use of such amides appears attractive as masking agents of carboxyl functions in such reactions.

C. *o*-Bromophenylacetic Acid (3). Halogen–metal interchange in *o*-bromophenylacetic acid is more complex owing to trianion formation (23) and incomplete halogen–metal exchange; however, by utilizing "anion decay" (see below), reasonable yields of elaborated products (**24**) can be obtained. Results of these studies, which are summarized in Scheme IV, have led us to the following conclusions and comments.

Scheme IV



1. Metalation of the rapidly formed salt **18** with the second equivalent of *n*-butyllithium was slow at −100°[4e] and leads to the dilithio derivative **21** and presumably to the trilithio derivative **23**. Whether **19** is formed at all, or whether it was unreactive owing to solubility or steric reasons, was not determined; however, no products derived from **19**, other than recovered **3**, were obtained in subsequent reactions. Examination of aliquots which were quenched with dilute acid showed no change in degree of metalation (ratio of *o*-bromophenylacetic acid to phenylacetic acid 36:64) after 4 hr.[4b]

2. The salt **19**, if formed, does not undergo appreciable further metalation. Addition of a third equivalent of *n*-butyllithium changed the above ratio to 30:70; however, further addition of *n*-butyllithium (up to 6 equiv) caused no appreciable further change in this ratio, and in the amount of *o*-bromophenylacetic acid recovered.

3. The dilithio derivative **21** does react with *n*-butyllithium to give the trilithio derivative **23**; however, **23** is unstable at −100° and reacts with solvent to regenerate **21**. Thus, addition of additional *n*-butyllithium has little effect on the ultimate composition of the mixture; **23** is formed from **21**, which decays back to **21**, and this process is repeated by addition of additional *n*-butyllithium.

4. The dilithio derivative **21** reacts with cyclohexanone by addition to give, subsequent to acidification, lactone **24**, and undoubtedly some phenylacetic acid by enolate formation with the ketone. Maximum yield of lactone **24** (42%, 60% based on converted **3**) was obtained when a mixture of *o*-bromophenylacetic and 3 equiv of *n*-butyllithium was stirred at −100° for 5 hr, to permit decay of **23** to **21**, prior to addition of excess cyclohexanone. The only other acids formed in this reaction were *o*-bromophenylacetic acid and phenylacetic acid (ratio 40:60).

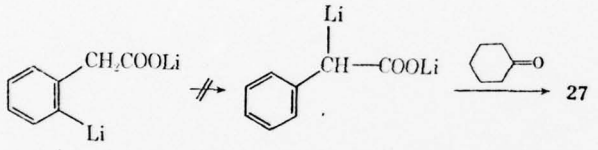
5. The trilithio derivative **23** reacts with cyclohexanone to give hydroxy acid **27**; in no case was hydroxy acid **25** detected. The anion **23** rapidly decays to **21** and after 4–5 hr at −75 to −100° is completely converted to **21**. Thus, if cyclohexanone is added only 1 hr after addition of the third equivalent of *n*-butyllithium to the reaction mixture obtained from **3** and 2 equiv of *n*-butyllithium (7 hr, −100°), **23** is present. Under these conditions hydroxy acid **27** is formed which was isolated in 39% yield; lactone **24** was isolated in 24% yield. If this solution is aged prior to addition of cyclohexanone (see 4, above), no hydroxy acid **27** is produced. The lifetime of **23** was examined (in separate experiments) by adding cyclohexanone after different time intervals following the addition of the third equivalent of *n*-butyllithium. The maximum yield of **27** (54%, 77% based on converted **3**) was obtained by adding excess cyclohexanone to an aged mixture (14 hr) prepared from **3** and 3 equiv of *n*-butyllithium 15 min after addition of a fourth equivalent of *n*-butyllithium; 10% yield of lactone **24** was also isolated in this case. Failure to isolate the disubstituted product **25** from the trilithio derivative is interpreted to mean that either (1) reaction with ketone occurred preferentially at the anion adjacent to carboxylate, and that the derived aryllithium intermediate **26** does not react further with cyclo-

hexanone for steric reasons, or (2) that the aryllithium in 26 is lost and converted to the salt of 27 by reaction with solvent. It is of interest to note that the corresponding trilithio derivative 30 derived from the para isomer reacts with cyclohexanone at both carbon anionic centers.

6. Loss of trilithio derivative 23 is a function of concentration and temperature. Reaction of 3 under identical conditions described in 5 (above), but at one-fourth the molar concentration (i.e., more concentrated in solvent tetrahydrofuran), led to greater loss of 23. The yield of 27 decreased from 39% to 26% while the yield of lactone derived from 24 increased from 24% to 30% (by isolation). Furthermore, addition of cyclohexanone to a mixture prepared from 3 (2 equiv of *n*-butyllithium) 3 hr after adding the third molar equivalent of *n*-butyllithium at −100° led to a 13% yield of 27, but to no 27 when the extra 3 hr of aging was at −75°.

7. An alternate pathway for the formation of 27 as shown in Scheme V is rejected. If this process was of signif-

Scheme V



icance, then aging prior to addition of cyclohexanone should result in an increase in yield of 27, which is in complete contradiction to the results observed.

Studies of metalation of *p*-bromophenylacetic acid (4) gave similar results and provided more conclusive evidence for formation of products derived from the trilithio derivative 30 (Scheme VI); however, the reaction products were more complex than those obtained from 3. The following observations were made.

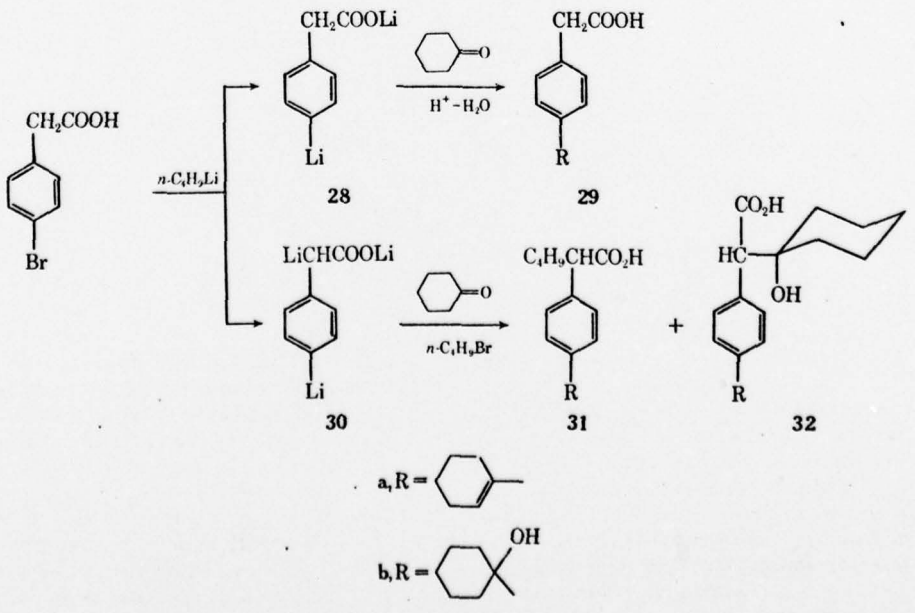
1. The degree of halogen–lithium interchange was 40% with 2 equiv of *n*-butyllithium after 2 hr and this value was unchanged after an additional 4 hr.[4c] The degree of halogen–lithium interchange decreased in more concentrated solutions. Thus, under similar conditions but at four times the molar concentration of 4 in solvent, the degree of halogen–lithium interchange was only 20%. This decrease is attributed to insolubility of the carboxylate salt of 4. The maximum degree of halogen–lithium interchange (60%) was achieved by addition of 3 equiv of *n*-butyllithium to 4 and stirring the resulting mixture (~17 hr). The solution was a mixture containing 28 and 30. The degree of halogen–lithium interchange was unchanged by addition of a fourth equivalent of *n*-butyllithium.

2. The trilithio derivative 30, like the analogous salt 23, decays to dilithio derivative 28 with time by reaction with solvent. Thus, addition of a fourth equivalent of *n*-butyllithium to a mixture prepared from 4 and 3 equiv of *n*-butyllithium gave a mixture rich in 30 relative to 28. When excess cyclohexanone was added 15 min after addition of the fourth equivalent of *n*-butyllithium, the product mixture contained little 29[9] which would be derived from the dilithium derivative 28. The acidic products were separated by preparative plate chromatography. The principal products were (a) an oil (~25% crude yield), the NMR spectrum of which was consistent with 31a (this product could not be induced to crystallize and was not characterized by composition analysis),[10] and (b) alcohol 32a (~25% crude yield) which was obtained pure.

In contrast, when the above solution was aged for 12 hr at −75°, there was considerable loss of trilithio derivative 30 to dilithio derivative 28. In this case, addition of excess cyclohexanone led to a significant quantity (~33% crude yield) of 29b. Chromatography of the mixed acids gave, in addition to 29b, products derived from the trilithio derivative 30 but in reduced yields: (a) diol 31b (~16% yield) which was obtained pure, and (b) a mixture (by NMR spectral analysis) of 32a and 32b (~16% total yield) which was not resolved.

3. Alkylations of lithium derivatives derived from 4 by *n*-butyl bromide formed during halogen–lithium exchange, to give products of type 31, detract from the synthetic utility of such syntheses with *p*-bromophenylacetic acid, an observation in sharp contrast to that observed with *o*-bromo-

Scheme VI



phenylacetic acid. We currently believe, but have not established, that alkylation at −100° occurs only with the very reactive trianion **30**, a process which is sterically inhibited with the ortho isomer **23**; consequently, we believe that significant amounts of alkylation at −100° will be encountered only in the phenylacetic acid series (meta or para).

While some exceptions have been defined, notably *p*-bromophenylacetic acid, the procedures described in A–C (above) offer useful routes for the elaboration of a seemingly broad variety of types of bromoalkanoic acids.

Experimental Section

A. Conversion of β-(*p*-Bromophenyl)propanoic Acid (1) to Phenylacetic Acid. β-(*p*-Bromophenyl)propanoic acid[11a] (2.29 g, 0.01 mol), mp 137–138° (lit.[11b] mp 136°), tetrahydrofuran (~125 ml, freshly distilled over lithium aluminum hydride), and dry hexane[13] (25 ml) were introduced, under nitrogen, into a three-neck flask equipped with a low-temperature thermometer, addition funnel, and nitrogen inlet tube. The reaction mixture was cooled to −100° (liquid nitrogen–diethyl ether bath) and *n*-butyllithium (9.2 ml, 0.022 mol, 2.4 *M* solution) was added rapidly (the rate of addition was adjusted such that the temperature did not exceed −90°). The reaction mixture was stirred at −100° for 45 min and poured into dilute aqueous hydrochloric acid (~50 ml). The organic layer was separated and the aqueous layer was extracted with four 100-ml portions of ether. The ether extracts were combined and extracted with two 50-ml portions of 10% aqueous sodium hydroxide. The aqueous basic extracts were combined, cooled, and added to cold dilute aqueous hydrochloric acid; the resulting mixture was extracted with four 100-ml portions of ether. The ether extracts were combined, dried ($MgSO_4$), and concentrated (rotary evaporation) to afford 1.55 g of light yellow semisolid. This material was distilled to give 1.29 g (86% yield, mp[12] and mmp 45–46°) of pure phenylacetic acid (**6**). The residue (0.26 g) was shown (NMR) to be a mixture of **1**, **6**, and a small amount of butylated acid (position of butyl group undetermined).

B. Preparation of β-(*p*-1-Cyclohexenylphenyl)propanoic Acid (7). Reaction of **1** (0.02 mol) in a mixture of THF (250 ml)–hexane[13] (50 ml) with *n*-butyllithium (0.044 mol) was carried out as in A. Cyclohexanone (0.10 mol) in dry hexane[13] (10 ml) was added; the mixture was warmed to 25° and poured into dilute hydrochloric acid (250 ml). The organic layer was extracted (four 150-ml portions) with ether. The acid, obtained by extraction of the ether extract with alkali, weighed 3.9 g (white solid, mp 105–112°). This material was sublimed [80° (0.01 Torr), 24 hr] to remove unchanged **1** (0.49 g, mp[11] and mmp 133–135°); the residue (3.1 g, 67% yield, mp 114–117°) was nearly pure **7**. Pure **7** (2.7 g, 59% yield from petroleum ether[14a]–chloroform) had mp 117–118°; NMR ($CDCl_3$) δ 1.72 (m, 4, aliphatic CH_2), 2.28 (m, 4, allylic CH_2), 2.72 (m, 2, CH_2Ar), 3.00 (m, 2, CH_2COOH), 6.23 (m, 1, vinyl H), 7.40 (m, 4, aromatic H), ~11.0 (broad s, 1, OH).

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.32; H, 7.80.

The residue (0.55 g) from the recrystallization of **7** was a mixture of phenylpropanoic acid (0.4 g, 13%) and unchanged **1**.

C. Indanones. 1. From β-(*o*-Bromophenyl)propanoic acid[15] (2). Reaction of **2** [0.01 mol, mp 99–101° (lit[17] mp 98°)] in THF (125 ml)–hexane[13] (25 ml) with *n*-butyllithium (0.02 mol) was carried out as in A; the reaction mixture was stirred for 3 hr at −100°. From the neutral component of the reaction product there was obtained 1.0 g [76% yield; bp 60–65° (0.2–0.15 Torr); mp and mmp[16a] 42°; mp of 2,4-dinitrophenylhydrazone 256–257° (lit.[16b] mp 258°)] of pure indanone (**9**).

The reaction was repeated at −78°; examination of aliquots showed that the reaction was faster and complete after only 30 min. The yield of isolated indanone was 77%.

2. From 3-*o*-Bromodiisopropylamide (13). Amide **13** [0.01 mol, bp 130–140° (0.02–0.01 Torr); 96% yield from 3-*o*-bromophenylpropanoyl chloride[17] and diisopropylamine in ether] in THF (125 ml)–hexane[13] (25 ml) was allowed to react with *n*-butyllithium (0.01 mol) as in A. Examination of aliquots[4] by NMR showed that after 1 hr at −100° the reaction product was indanone contaminated with a small amount of butylated material. The mixture was quenched with water and the dried material obtained from the ether extract was distilled to give 0.8 g (61% yield) of pure indanone.

3. 2-(*o*-Bromobenzyl)-1-indanone (12). The starting acid **10** (mp 152–153°) was prepared in high yield from crude diethyl di(*o*-bromophenyl)malonate (by hydrolysis and decarboxylation of the derived malonic acid) obtained as a by-product in the synthesis of **2** from *o*-bromobenzyl bromide and diethyl malonate.

Anal. Calcd for $C_{16}H_{14}Br_2O_2$: C, 48.27; H, 3.54; Br, 40.15; neut equiv, 398. Found: C, 48.03; H, 3.67; Br, 39.94; neut equiv, 396.

Reaction of **10** (0.02 mol) with *n*-butyllithium (2 equiv) in THF (300 ml) and hexane[13] (50 ml) was carried out as in C-1 and gave 4.1 g (66% yield) of pure 2-(*o*-bromobenzyl)-1-indanone (**12**), bp 165–170° (0.05–0.04 Torr).

Anal. Calcd for $C_{16}H_{13}BrO$: C, 63.80; H, 4.35; Br, 26.54. Found: C, 63.96; H, 4.28, Br, 26.61.

4. 2-Benzyl-1-indanone. Reaction of **10** with *n*-butyllithium (3 equiv) was carried out as described in C-3 above. Distillation of the crude product gave 3.2 g (72% yield) of pure 2-benzyl-1-indanone, bp 135–140° (0.03 Torr).

Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 87.70; H, 6.35.

D. Reactions of β-(*o*-Bromophenyl)propionamide (14). 1. Conversion to Phenylpropionamide. Amide **14**[18] (0.01 mol) was treated with *n*-butyllithium (0.02 mol) in THF (125 ml)–hexane[13] (25 ml) as described in A. An aliquot (25 ml) taken after 30 min at −100° was quenched with water; NMR analysis showed only 3-phenylpropionamide.[4d] The mixture was quenched with water, and the crude product obtained by extraction with ether was recrystallized from water to give 1.22 g (81% yield) of pure 3-phenylpropionamide (mp and mmp[19] 104–105°).

2. Conversion to *o*-(1-Hydroxycyclohexyl)-3-phenylpropionamide (17). The reaction was carried out as in D-1 above, and quenched after 30 min with cyclohexanone (0.04 mol) in dry hexane[13] (20 ml) at −100°. The crude product (5.5 g) obtained after addition of water and extraction with ether and containing cyclohexanone was recrystallized from petroleum ether[14a] to give 2.1 g of white solid which was a mixture of **16** and **17**. This material was chromatographed on silica gel (200 g). Elution of the column with petroleum ether[14a]–ether (70:30) gave 0.88 g (59% yield) of 3-phenylpropionamide; elution with petroleum ether[14a]–ether (50:50) gave 1.1 g of white solid which was recrystallized from chloroform–petroleum ether to give 0.97 g (40% yield) of pure **17** (mp 148–150°).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 73.00; H, 8.42; N, 5.49.

E. Metalation of *o*-Bromophenylacetic Acid (3) with *n*-Butyllithium. 1. Degree of Metal–Halogen Exchange. Reaction of **3**[20] (0.025 mol) with *n*-butyllithium (0.05 mol) in THF (150 ml) and hexane[13] (30 ml) was carried out as in B. Examination of an aliquot[4c] (10 ml) taken after 30 min at −100° showed that the degree of halogen–metal exchange [ratio of *o*-bromophenylacetic acid (**3**) to phenylacetic acid (**22**)] was 50:50. The ratio of **3** to **22** was 40:60 after an additional 1 hr; after an additional 2.5 hr the ratio was 36:64 and this ratio did not change after an additional 2 hr at −100°.

A third molar equivalent of *n*-butyllithium was added to the reaction mixture at −100°; and the mixture was stirred for an additional 1 hr at −100°. Examination of an aliquot (10 ml) showed that the ratio of **3** to **22** was 30:70. Additional reaction time (at −100°) and/or further addition of *n*-butyllithium (up to a total of 6 molar equiv) caused no appreciable change in the above ratio (30:70).

Examination of aliquots from a similar reaction but at −78° (instead of −100°) showed no appreciable change in the progress and/or degree of metalation.

Synthesis of Spirolactone 24. Metalation of *o*-bromophenylacetic acid[21] (5.4 g, 0.025 mol) was effected with *n*-butyllithium (0.075 mol) as described above. The mixture was aged for 5 hr at −95 to −100° (ratio of *o*-bromophenylacetic acid to phenylacetic acid 30:70 by NMR spectral analysis)[4c] and cyclohexanone (9.8 g, 0.1 mol) in hexane (20 ml) was added to the mixture maintained at −100°. The resulting mixture was allowed to warm to room temperature and was added to a mixture of ether (200 ml) and aqueous sodium hydroxide (200 ml, 5%). The two layers were separated and the aqueous layer was extracted with ether (four 100-ml portions). The basic layer containing the salt of **24** was acidified (hydrochloric acid), brought to boil, cooled, and extracted with ether (400 ml). The ether extract was cooled (0–5°) and extracted with cold (0–5°) aqueous sodium hydroxide (100 ml, 3%). The ether layer was washed with cold water (50 ml), dried ($MgSO_4$), and concentrated to give nearly pure **24** (2.3 g, 42% yield, mp 95–105°; 2.1 g, 39% yield, mp 105–106° from petroleum ether[14b]).

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.96; H, 7.40.

The NMR spectrum of the acid material (2.2 g) obtained from the alkaline extract showed it to be a mixture of *o*-bromophenylacetic acid (**3**) and phenylacetic acid (**22**) in the ratio 40:60 (20 and 33% yield, respectively).

Preparation of Hydroxy Acid 27. The reaction was conducted as described for **25** *with the following modifications. The mixture* was stirred for 7 hr after addition of 2 equiv of *n*-butyllithium, but only 15 min after addition of the third equivalent of *n*-butyllithium prior to addition of cyclohexanone. The yield of lactone **24** (mp and mmp 105–106°) was 10%.

Concentration of the dried ether extract obtained from the acidified alkaline extract gave a mixture of **27**, *o*-bromophenylacetic acid (**3**), and phenylacetic acid (**22**). Fractional crystallization of the product from chloroform–petroleum ether[14c] gave 2.92 g of pure **27** (54% yield, mp 114–146°).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.95; H, 8.00.

F. Reactions of *p*-Bromophenylacetic Acid (4). 1. Reaction of *p*-bromophenylacetic acid (5.4 g, 0.025 mol) was carried out exactly as described for **3** except the temperature was −78°[4b] (Dry Ice–acetone bath). Progress of metalation was followed as for **3**.[4c]

The ratio of recovered *p*-bromophenylacetic acid to phenylacetic acid was 60:40 after 2 hr and the ratio did not change after an additional 2–4 hr. An additional molar equivalent of *n*-butyllithium was added and the mixture was stirred at −78° for 17 hr. An aliquot showed the above ratio of acids to be 40:60. A fourth equivalent of *n*-butyllithium was added, and after 15 min at −78° an excess of cyclohexanone (5 equiv) dissolved in hexane (35 ml) was added rapidly. The mixture was allowed to warm to room temperature and was then partitioned between aqueous sodium hydroxide (100 ml, 10%) and ether (100 ml). Acidification of the alkaline layer (hydrochloric acid) gave 6.22 g of acidic product as a semisolid which was collected by ether extraction. Elution of the mixed acids (600 mg) from a preparative silica gel plate (fluorescent indicator) with a mixture of petroleum ether[14a] and ether (80:20) gave two major fractions. (1) 160 mg (~25%, higher R_f) of an oil. The NMR spectrum ($CDCl_3$) of this product was consonant with slightly impure **31a**: δ 0.9 (t, 3, CH_3), 1.25–2.3 (m, 1, aliphatic H), 3.55 (broad t, 1, benzylic methine), 6.2 (m, 1, vinyl H), 7.4 (broad, 4, aromatic H). This material could not be induced to crystallize and was not purified.[10] (2) 300 mg (lower R_f) of an oil. This product was rechromatographed as above, to give one major fraction (180 mg, ~25% yield) of an oil, the NMR spectrum ($CDCl_3$–DMSO-d_6) of which suggested that it was **32a** [δ 0.9–2.0 (m, 16, aliphatic H), 2.15–2.58 (m, 2, allylic H)]. The material crystallized from chloroform and melted at 193–200° dec.

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.17; H, 8.49.

2. The reaction was carried out as above except that the mixture was aged for 12 hr prior to addition of excess cyclohexanone. Analysis of an aliquot, as discussed in the text, showed that the ratio of acids remained constant at 40:60. A portion (580 mg) of the mixed acids (5.8 g, yellow semisolid) was purified by preparative plate chromatography (as in F-1) to give three major bands. (1) 180 mg (~33% yield) of an oil (higher R_f), the NMR spectrum of which was consistent with alcohol **29b**: NMR ($CDCl_3$) δ 1.4 (broad m, 10, aliphatic H), 3.6 (broad s, 2, benzylic methylene), 7.4 (broad m, H, aromatic H). The material crystallized from chloroform, mp 134–136°.

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 72.00; H, 8.00.

(2) 120 mg (~16% yield) of an oil (medium R_f) whose NMR spectrum was consistent with **31b**: NMR ($CDCl_3$) δ 1.0 (t, 3, $-CH_3$), 1.6 (m, 16, aliphatic H), 3.7 (t, 1, benzylic methine), 6.8 (broad s, 1, –OH), 7.6 (m, 4, aromatic H). This material crystallized from chloroform, mp 110–114°.

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.66; H, 8.86.

(3) 130 mg (~16% yield) of an oil (lower R_f) which was not resolved; however, the NMR spectrum was consistent with **32b** contaminated with **32a**. Compound **32a** was characterized in the preceding experiment.

Registry No.—**1**, 1643-30-7; **2**, 15115-58-9; **3**, 18698-97-0; **4**, 1878-68-8; **7**, 55223-22-8; **9**, 83-33-0; **10**, 55223-23-9; **12**, 55223-24-0; **13**, 55223-25-1; **14**, 55223-26-2; **17**, 55223-27-3; **24**, 55223-28-4; **27**, 5449-68-3; **29b**, 55223-29-5; **31a**, 55223-30-8; **31b**, 55223-31-9; **32a**, 55223-32-0; **32b**, 55223-33-1; diethyl di-(*o*-bromophenyl)malonate, 55223-34-2; 2-benzyl-1-indanone, 16307-30-5.

References and Notes

(1) Supported by the U.S. Army Research Office through Grant DAHCO4 74 GD128.

(2) A. J. Meyers and D. L. Temple, Jr., *J. Am. Chem. Soc.*, **92**, 6646 (1970).

(3) (a) W. E. Parham and Y. A. Sayed, *J. Org. Chem.*, **39**, 2051 (1974); (b) *ibid.*, **39**, 2053 (1974).

(4) In general, 0.02 mol of acid in ~300 ml of solvent was employed; aliquots of 10 ml were quenched with water and the organic material was extracted with ether. The extract was concentrated to give sample for NMR analysis. In many cases, neutral components were separated from acids by conventional extraction procedures and analyzed separately by NMR. (a) *p*-Bromophenylpropanoic acid (A, A′, B, B′ aromatic pattern) could easily be differentiated from phenylpropanoic acid (simple singlet for aromatic protons); however, the absorptions overlapped so that only estimates of composition were possible. (b) *o*-Bromophenylacetic acid and phenylacetic acid show benzylic methylenes at δ 3.8 and 3.60 (60 MHz), respectively. The ratio of these two acids is based on integrations of these two absorptions. (c) *p*-Bromophenylacetic acid shows benzylic methylene at δ 3.56, sufficiently resolved from phenylacetic acid (δ 3.60) to permit accurate analysis. (d) 3-(*o*-Bromophenyl)propionamide shows a complex pattern for the aromatic protons (δ 6.9–7.7) while 3-phenylpropionamide shows only a single peak at δ 7.1. (e) Similar results were obtained at −78°. (f) Similar results were obtained at −100°.

(5) The position of the butyl group was not determined.

(6) Part of the aryllithium reagent is reduced by proton abstraction to give the enolate of cyclohexanone; cyclohexanone was chosen for elaboration of **5** since we felt that the yields of products would provide a more realistic evaluation of the synthetic utility of the process than would use of nonenolizable carbonyl functions.

(7) (a) Possible application of this reaction for the syntheses of tetralones and related materials is being investigated. (b) Indanones are usually prepared by cyclization of arylpropanoic acids. The method described in this report obviates isomers encountered by direct cyclization of unsymmetrically substituted arylpropanoic acids; furthermore, Friedel–Crafts type cyclization cannot be employed when the aryl group is substituted with meta-directing groups.

(8) This observation supports the conclusion that both bromine atoms in **10** undergo metal exchange prior to cyclization when 3 equiv of *n*-butyllithium is employed. The product (**12** with bromine replaced by lithium) reacts with itself by enolization of carbonyl rather than addition to carbonyl, probably because of unfavorable entropy considerations for addition.

(9) (a) Compounds **29a,b** were not detected upon preparative plate chromatography; however, conversion of an aliquot of the products to the methyl esters (with diazomethane) with subsequent GLC and NMR analysis showed that **29a** and/or **29b** (detected as **29a**) was present in very low yield.

(10) In a subsequent experiment the hydroxy acid **31b** was obtained pure and was characterized by compositional analysis (see Experimental Section).

(11) (a) This acid was prepared from *p*-bromobenzyl chloride by a malonic ester synthesis similar to that reported for the preparation of α-bromo-β-phenylpropionic acid: C. Marvel, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 705. (b) S. Gabriel and J. Zimmerman, *Chem. Ber.*, **13**, 1683 (1880).

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(13) Practical grade stored over molecular sieves.

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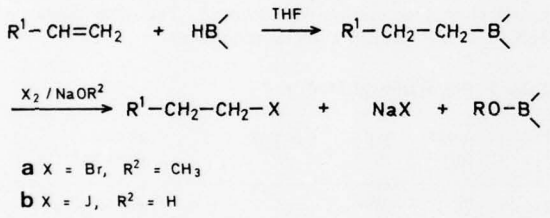
in the earlier procedure involving sodium hydroxide as the base.

The usually sluggish reactions of trialkylboranes with bromine[2] and with iodine[3] are greatly accelerated by the presence of methanolic sodium methoxide and sodium hydroxide, respectively. These results provide highly convenient procedures for the *anti*-Markovnikov hydrobromination and hydroiodination of olefins.



The bromination procedure utilizes all three boron bound groups of trialkylboranes derived from the hydroboration of terminal olefins and two groups of trialkylboranes from internal and cyclic olefins. Unfortunately, however, the earlier iodination procedure utilizes only two groups from primary alkyl organoboranes and only one group from secondary alkyl organoboranes. The lower conversion realized in the iodine reaction could severely limit the synthetic utility of the reaction if a valuable olefin were to be converted into the corresponding iodide.

In this study we have established that the substitution of sodium methoxide as the base in the reaction of organoboranes with iodine greatly improves the yields of the alkyl iodides.

When trialkylboranes derived from the hydroboration of terminal olefins are treated with iodine and sodium methoxide, two of the groups on boron react virtually instantaneously. The third group reacts more slowly (Table 1).

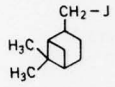
Table 1. The Reaction of Tri-*n*-butylborane with Iodine and Sodium Methoxide at 25°[a]

Time (hours)	Yield (%)[b] of n-C_4H_9J
0.1	65
1	68
4	75
24	79
36	80
72	83

[a] Reaction of tri-n-butylborane (10 mmol) with J_2 (30 mmol) and $NaOCH_3$ (30 mmol).

[b] Yield determined by G.L.P.C.; conditions: 10% Dow Corning 710 on Chromosorb W; column 6 ft × 0.25 in.

Table 2. Conversion of Olefins into Alkyl Iodides *via* Hydroboration-Iodination[a]

Olefin	Product[b]	Reaction time	Yield (%)[c] NaOH[d]	Yield (%)[c] $NaOCH_3$
$H_2C{=}CH{-}CH_2{-}CH_3$	n-C_4H_9-J	24 h	65	79
$H_2C{=}C(CH_3){-}CH_3$	i-C_4H_9-J	24 h	63	80
		24 h	60	72
$H_2C{=}CH{-}(CH_2)_8{-}COOCH_3$	$J{-}CH_2{-}(CH_2)_9{-}COOCH_3$	24 h	—	80 (68)
$H_3C{-}CH{=}CH{-}CH_3$	$H_3C{-}CH(J){-}CH_2{-}CH_3$	3 h	30	66
		3 h	33	64
		3 h	—	72

[a] Reaction of R_3B (10 mmol) with J_2 (30 mmol) and $NaOCH_3$ (30 mmol) for the time indicated.

[b] All products characterized by comparison with authentic samples.

[c] Yields, based on starting olefin, determined by G.L.P.C. (conditions: 10% Dow Corning on chromosorb W; 6 ft × 0.25 in); value in parentheses refers to isolated product.

[d] Taken from reference 2.

In the case of trialkylboranes derived from internal and cyclic olefins, two of the groups react rapidly with the iodine. The third group resists reaction at 25°, even over extended periods of time. The experimental results are summarized in Table 2.

Conversion of Methyl 10-Undecenoate to Methyl 11-iodoundecanoate[4]:

A dry 500-ml flask equipped with septum inlet, magnetic stirrer, and gas connecting tube was flushed with dry nitrogen and maintained under a static pressure of the gas until workup. The flask was charged with tetrahydrofuran (100 ml) and methyl 10-undecenoate (33.7 ml, 150 mmol and cooled to 0° in an ice bath. Conversion to the trialkylborane was achieved by the dropwise addition of neat borane-methyl sulfide[5] (5.10 ml) over 40 minutes. The ice bath was removed and the reaction was allowed to stir one hour at room temperature. Then absolute methanol (1 ml) was added to destroy traces of residual hydride. Iodine (38.1 g, 150 mmol) was added all at once, followed by the dropwise addition of a solution of sodium methoxide in methanol (31.8 ml of a 4.72 *M* solution, 150 mmol) over a period of 10 minutes. The reaction mixture was allowed to stir 24 hours. G.L.P.C. analysis of the reaction mixture using *n*-decane for an internal standard indicated an 80% yield of methyl 11-iodoundecanoate. A saturated aqueous sodium thiosulfate solution was poured into the reaction mixture until the excess iodine was decolorized. The reaction mixture was extracted with pentane (100 ml) and dried over anhydrous magnesium sulfate. Distillation under vacuum gave methyl 11-iodoundecanoate: yield: 33.1 g (68%); b.p. 139–141°/0.15 torr; $n_D^{20} = 1.4856$; 99% pure by V.P.C.[6].

These results suggest that the alkali induced reactions of many other electrophilic reagents with organoboranes may be even more strongly facilitated by sodium methoxide.

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* Author to whom correspondence should be addressed.

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[5] Available from the Aldrich Chemical Company. Very similar results were obtained using borane-tetrahydrofuran.

[6] Exhibited physical data consistent with assigned structure; V.P.C. conditions: 10% Dow Corning on Chromosorb W; 6 ft × 0.25 in.

Synthesis of Indenes and 1,2-Dialkylbenzenes[1]

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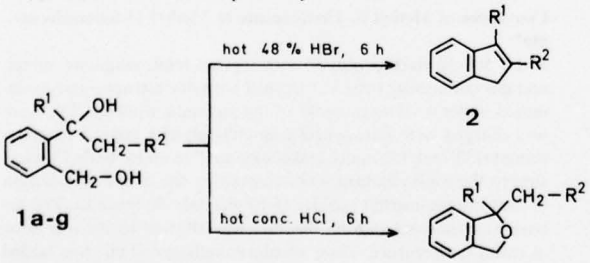
We have had a continuing interest in the synthesis of indenes[2] in view of their use as starting materials for the preparation of aromatic systems[3]. It is known[2a] that diols of type **1c**, prepared from 2-bromobenzyl alcohol and cyclic ketones, can be converted efficiently to indenes by reaction with boron trifluoride; however, this procedure is not effective[2b] for diols prepared from acyclic ketones. We have now observed that excellent yields of 2,3-disubstituted indenes (**2**) are generally obtained by reaction of the readily available diols[2] **1** with hot 40% hydrobromic acid (6 h). The procedure is considerably more convenient and gives higher yields of purer products than the alternative sequence involving reaction of the monoacetate of **1** with formic acid/acetic anhydride[2b]. The yields of isolated, pure **2a**[4], **2b**, and **2c** were 84%, 79%, and 81%, respecitvely.



	R^1	R^2
a	CH_3	CH_3
b	C_2H_5	CH_3
c	$-(CH_2)_4-$	
d	H	CH_3
e	CH_3	H
f	C_6H_5	H
g	H	H

The procedure is not useful for the preparation of 2- or 3-monoalkylindenes, since complex mixtures result which contain indenes, phthalans, and higher molecular weight condensation products. Mono-arylindenes can, however, be prepared, but not as efficiently as the disubstituted indenes. The highest yield of **2f** isolated was 52%; 1-(2-bromomethylphenyl)-1-phenylethene and polymeric material were also formed in this reaction.

Reaction of diols of type **1** with hot concentrated hydrochloric acid (6 h) gives phthalans (**3a–g**) in nearly quantitative yields, while similar reactions with hot 48% hydroiodic acid[5,6] (6 h) gives, with certain diols, excellent yields of 1,2-dialkylbenzenes. The yields of 1-phenyl-1-(2-methylphenyl)-ethane isolated from the reaction of **1f**, 2-*i*-propyltoluene from **1e**, and 2-*n*-propyltoluene from **1d** were 92%, 62%, and 73%, respectively; however, formation of hydrocarbon from **1d** was slow and required 12 h of reflux. By contrast, reaction of benzyl alcohol with hot 48% hydroiodic acid gave almost exclusively benzyl iodide, while reaction of **1a** (6 h) gave 2,3-dimethylindene (52% yield) together with polymeric material; no detectable reduction to hydrocarbon was observed in the latter case.

In summary, the synthesis outlined above with 48% hydrobromic acid is the procedure of choice for the preparation of a variety of 2,3-disubstituted indenes from diols **1**.

Preparation of Diols 1:

Diols **1a**, **1b**, and **1f** were prepared (80–83% yields) from *o*-bromobenzyl alcohol as previously described[2b]. The diols shown in Table 1 were prepared by similar procedures.

Table 1. Preparation of Diols **1**

Diol	Yield (%)	m.p.	b.p./torr	Brutto formula[a]
1c	74	69°[b]	—	$C_{13}H_{18}O_2$ (206.29)
1d	66	—	105–107°/0.02	$C_{10}H_{14}O_2$ (166.22)
1e	60	—[c]	145–150°/4	$C_{10}H_{14}O_2$ (166.22)
1g	62	—	115–118°/0.05	$C_9H_{12}O_2$ (152.19)

[a] All diols gave satisfactory elemental analyses (C ± 0.18%, H ± 0.14%).

[b] Recrystallized from ether/petroleum ether[7].

[c] Lit.[8] m.p. 63–64°.

Preparation of Indenes 2; General Procedure:

A mixture of the diol **1** (0.02 mol) and 48% hydrobromic acid (20 ml) was heated at the reflux temperature for 6 h. The cooled mixture was diluted with water (100 ml), extracted with ether (3 × 100 ml), and the combined ether extracts were washed with aqueous saturated sodium hydrogen carbonate solution and then with water. The dried ($MgSO_4$) extract was concentrated and the indene was either distilled or crystallized (see Table 2).

The mixture derived from **1f** was purified by column chromatography (alumina, 500 g, petroleum ether[7] as eluent); the two major products were distilled to give *3-phenylindene* (**2f**, see Table 2) and *1-(2-bromomethylphenyl)-1-phenylethene*; yield: 33%; b.p. 109–114°/0.5 torr.

$C_{15}H_{13}Br$	calc.	C 65.95	H 4.80	Br 29.25
(273.18)	found	65.86	4.84	29.23

^{1}H-N.M.R. ($CDCl_3$): δ = 4.3 (s, $-C\underline{H}_2Br$), 5.3 (d, $=C\underline{H}-$), 5.8 (d, $=C\underline{H}-$), 6.9–7.2 ppm (m, $9H_{arom}$).

Analysis of the product from **1e** by ^{1}H-N.M.R. showed it to be a mixture of *3-methylindene* (**2e**), *1,1-dimethylphthalan* (**3e**), and a *bromoalkene* as evidenced by the benzylic methylene absorptions ($CDCl_3$) at 3.2 (m), 5.0 (s), and 4.5ppm (s), respectively.

When **1e** was treated for 30 min with cold 48% hydrobromic acid, pure *1,1-dimethylphthalan*[11] (**3e**) is obtained; yield: 96%; b.p. 48–51°/2 torr.

Table 2. Preparation of Indenes **2**

Product	Yield (%)	b.p./torr	m.p.	^{1}H-N.M.R.	Reference
2b	79	67–70°/0.05	—	—[2b]	2b
2a	84	53–55°/0.5	—	—[2b]	9
2c	81	92–95°/0.2	54–56°[a]	—	3b
2f	52	92–95°/0.2	—	—[2b]	9, 10

[a] Mixture melting point: 54–56°.

Preparation of Phthalans 3:
Reactions of **1a**, **1b**, and **1f** with hot concentrated hydrochloric acid were carried out as described for hydrobromic acid. Phthalans **3a**, **3b**, and **3f** were the only products detected and were isolated[2b] in >80% yield.

Reductions with 48% Hydroiodic Acid; General Procedure:
A mixture of 1-(2-hydroxymethylphenyl)-1-phenylethanol (**1f**: 4.56 g, 0.02 mol) and 48% hydroiodic acid (20 ml) was heated at the reflux temperature for 6 h; the mixture was then processed as described in the general procedure for reactions with hydrobromic acid to give pure 1-phenyl-1-(2-methylphenyl)-ethane; yield: 92%, b.p. 74–75°/0.1 torr; (lit.[12] b.p. 99–101°/1 torr).

$C_{15}H_{16}$	calc.	C 91.78	H 8.22
(196.29)	found	*91.67*	*8.66*

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.5$ (d, $>CH-C\underline{H}_3$), 2.1 (s, $-C_6H_4-C\underline{H}_3$-2), 4.2 (q, $-C\underline{H}-CH_3$), and 6.9–7.3 ppm (m, $9H_{arom}$).

Similarly prepared were:
From **1e**, *2-isopropyltoluene*[13]: yield: 62%; b.p. 68–71°/20 torr.
^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.1$ (d, $C\underline{H}_3$), 2.2 (s, $-C_6H_4-C\underline{H}_3$), 3.0 (m, $\geqslant C\underline{H}$), and 6.8–7.4 ppm (m, $4H_{arom}$).

From **1d**, *2-n-propyltoluene*[14]: yield: 73%; b.p. 78–80°/20 torr.
^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.0$ (t, CH_3), 1.5 (m, $-CH_2-C\underline{H}_2-CH_3$), 2.3 (s, $-C_6H_4-C\underline{H}_3$), 2.6 (t, $-C_6H_4-C\underline{H}_2-$), and 7.0 ppm (m, $4H_{arom}$).

The latter reaction was slow and required a 12 h reflux period to remove an intermediate, assumed to be 2-*n*-propylbenzyl iodide (^{1}H-N.M.R.: $\delta = 4.4$ ppm (s, $-C_6H_4-C\underline{H}_2-J$)).

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[1] Supported by the United States Army Research Office through Grant DAHCO4 74 GD128.

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Nicht-nucleophile Alkoholate als Hilfsbasen

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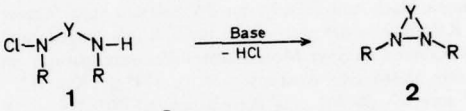
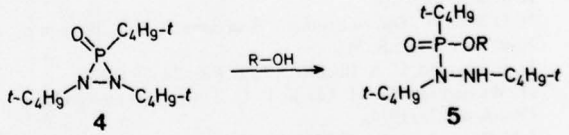
Für zahlreiche Reaktionen benötigt man möglichst nicht-nucleophile, starke Hilfsbasen[1]. Das gilt besonders für 1,3-Eliminierungen zu empfindlichen Produkten wie Cyclopropanonen[2], Aziridinonen[3], Diaziridinonen[4] und entsprechenden Iminen[5,6].



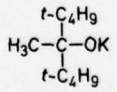
1 **2**

Y = —C(=O)— (Lit. 4), —C(=NR)— (Lit. 5), —SO_2— (Lit. 7), —P(=O)(C_4H_9-t)— (Lit. 8)

Die Anwesenheit einer N—Cl-Gruppe in der Ausgangsverbindung (**1**) verbietet die Verwendung oxidierbarer Hilfsbasen[1,9,10,11]. Die bisher gebräuchlichen tertiären Alkoholate[1] sind zwar kaum oxidierbar, aber immer noch zu nucleophil für sehr empfindliche Verbindungen; so erhält man aus **1**, Y = —P(O)(*t*-C_4H_9)—, mit Kalium-*t*-butanolat und selbst mit Kalium-3-äthyl-3-pentanolat nur Folgeprodukte (**5**) des Diazaphosphiridins **4** [= **2**, Y = —P(O)(*t*-C_4H_9)—, R = *t*-C_4H_9]. Dagegen gelingt die Isolierung von **4** glatt mit Kalium-2,2,3,4,4-pentamethyl-3-pentanolat[8] (**3**), das leicht aus dem entsprechenden Alkohol[12] mit Kaliumhydrid[13,14] in Tetrahydrofuran entsteht.



4 **5**

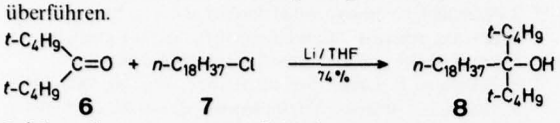


3

Unter den angewandten Bedingungen erweisen sich sowohl **3** als auch der Alkohol als inert gegenüber dem hochempfindlichen Diazaphosphiridin **4**.

Vorteilhaft für eine Reaktionskontrolle ist das einfache ^{1}H-N.M.R.-Spektrum von **3** bzw. dem entsprechenden Alkohol. Während die leichte Sublimierbarkeit dieses Alkohols in manchen Fällen für eine Isolierung der Produkte günstig sein dürfte, ist sie ein Nachteil, wenn man besonders reaktionsfähige Verbindungen wie das Diazaphosphiridin **4** durch Hochvakuumsublimation abtrennen muß. Ein für solche Zwecke besser geeigneter Alkohol (**8**) ist aus 2,2,4,4-Tetrame-

thylpentanon (**6**) und 1-Chlorooctadecan (**7**) leicht zugänglich[15] und läßt sich mit Kaliumhydrid glatt in das Alkoholat[8] überführen.



6 **7** **8**

Infolge seiner extremen Löslichkeitseigenschaften kann der Alkohol **8** leicht zurückgewonnen werden.

Die bei den vergleichbar sterisch gehinderten Tri-*sec*-alkylmethanolaten beobachtete Basizitätserhöhung infolge sterischer Effekte[14] dürfte auch bei den von **8** abgeleiteten Alkoholaten anzutreffen sein.

3-*t*-Butyl-2,2-dimethyl-3-hydroxyheneicosan (8):
Zu Lithium-Schnitzeln (3.46 g, 0.50 mol) in trockenem Tetrahydrofuran (120 ml) läßt man unter Stickstoff und gutem Rühren eine Mischung (~2 ml) von 1-Chlorooctadecan und 2,2,4,4-Tetramethylpentanon (Molverh. 2:1) tropfen und erwärmt leicht, bis das Lithium ein metallisch glänzendes Aussehen erhält. Dann läßt man unter Eiskühlung innerhalb 90 min die übrige Mischung aus Tetramethylpentanon (28.4 g, 0.2 mol) und 1-Chlorooctadecan (69.4 g, 0.24 mol) zutropfen und rührt noch einige Stunden bei 0°. Überschüssiges Lithium wird abfiltriert, das Lösungsmittel im Vakuum abdestilliert und der Rückstand in Petroläther (50–70°, 100 ml) aufgenommen. Nach Ausschütteln mit 2 *N* Salzsäure und Wasser wird mit Kaliumcarbonat getrocknet, im Vakuum eingedampft und der Rückstand in einer Molekulardestillationsapparatur im Hochvakuum destilliert; Ausbeute: 58.5 g (74%); Kp: 123–136°/10^{-5} torr; F: 28–30°; aus Petroläther (50–70°) bei −20° farblose Kristalle, Fp: 34–35°.

$C_{27}H_{56}O$	ber.	C 81.75	H 14.23
(396.7)	gef.	82.13	14.09

I.R. (ohne Lösungsmittel): $\nu_{max} = 3580\ cm^{-1}$ (OH).

^{1}H-N.M.R. ($CDCl_3$, 60 MHz): $\delta = 1.05$ (s, 2 *t*-C_4H_9), 1.26 ppm (breites s).

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Boron Compounds XLI[1]. Mixed Tetrasubstituted Ethenes via Organoborates

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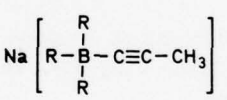
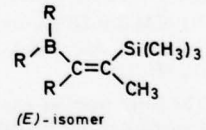
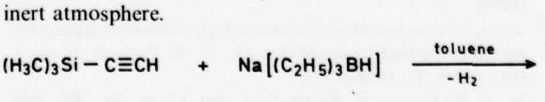
The reaction of alkali trialkylalkynylborates with various electrophilic reagents[2] has been used to synthesise a wide variety of substituted ethenes[3–6]. The synthesis usually yields a mixture of the (*Z*/*E*)-ethenes[2, 3]. However, the addition of chlorotrimethylsilane to sodium trialkylpropynylborates gives only one isomer, namely the (*E*)-2-trimethylsilylvinylboranes[4].





(E)-isomer

In order to investigate the novel directive effect of the silicon atom and to determine its applicability to the highly stereoselective synthesis of various 2-trimethylsilyl-substituted vinylboranes we have synthesised sodium triethyl(trimethylsilylethynyl)borate (**1**). Compound **1** is easily prepared from trimethylsilylacetylene[7] and sodium triethylborate[8] in toluene in yields of 70 to 90%. The white crystalline **1** is quite stable at room temperature when stored under an inert atmosphere.



1

The reaction of **1** with various electrophiles and the effect of the silicon atom on the stereochemistry of the final product was determined (see Scheme **A**) with the aid of ^{11}B-N.M.R. and ^{1}H-N.M.R.

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Selective Halogen–Lithium Exchange in Bromophenylalkyl Halides[1]

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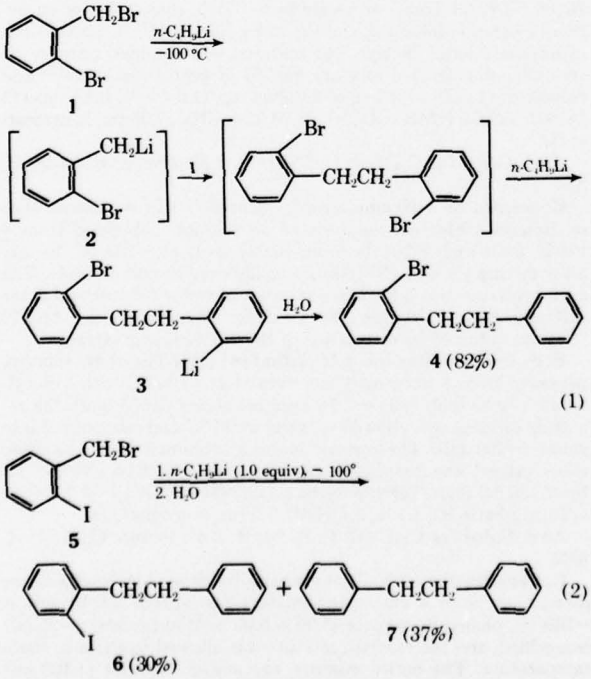
Halogen–metal exchange with a variety of bromophenylalkyl halides at low temperature (−100 °C) is selective and the order of exchange is $ArCH_2Br > ArBr > ArCH_2CH_2Br > Ar(CH_2)_nCl$. Thus, stable lithioaryl derivatives, which can be elaborated by addition of E^+, are obtained from *o*-bromobenzyl chloride, β-(*o*-bromophenyl)ethyl bromide, and γ-(*o*-bromophenyl)propyl chloride. Intramolecular cyclization occurs rapidly at −100 °C with γ-(*o*-bromophenyl)propyl bromide. Coupling occurs by primary benzylbromine–metal exchange with benzyl bromides. Attempts to prepare benzocyclopropene from *o*-lithiobenzyl chloride leads instead to 9,10-dihydroanthracene. A number of synthetic applications are discussed including a new, convenient synthesis of benzocyclobutene.

The success achieved for the elaboration of aryl bromides containing functional groups[2] that are normally reactive to alkyl- or aryllithium reagents by halogen–metal exchange at very low temperature (−100 °C) has prompted us to examine related reactions with aryl bromides containing haloalkyl functional groups. Complete selectivity has been observed and the order of halogen–metal exchange has been found to be $ArCH_2Br > ArBr > ArCH_2CH_2Br > Ar(CH_2)_nCl$. Halogen–metal exchange reactions were generally conducted at −100 °C in tetrahydrofuran–hexane with *n*-butyllithium. The course of reactions was followed by quenching aliquots with water and examining products both by NMR and by comparing GLC retention times with those of authentic samples, and subsequently by isolation of products.

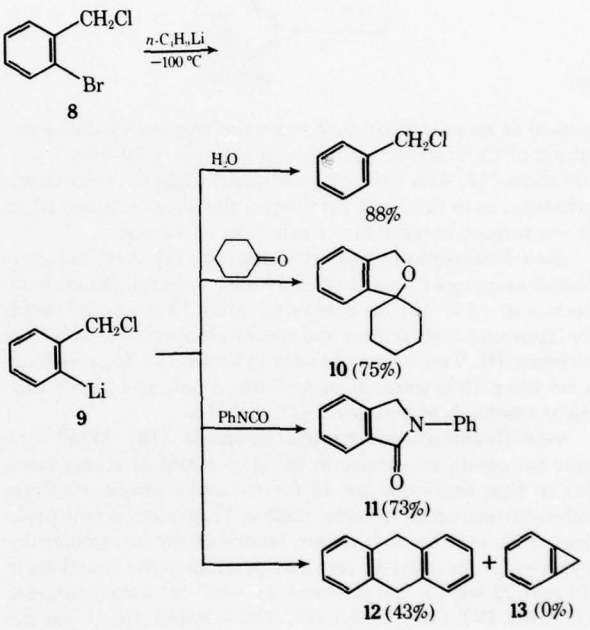
***o*-Bromobenzyl Bromide and *o*-Iodobenzyl Bromide.** Reaction of *o*-bromobenzyl bromide with 1 equiv of *n*-butyllithium gave 2-bromobibenzyl (**4**, 82% isolated yield) which is consistent with initial bromine–metal exchange at the benzyl bromide function as shown in Scheme I (eq 1).

Scheme I



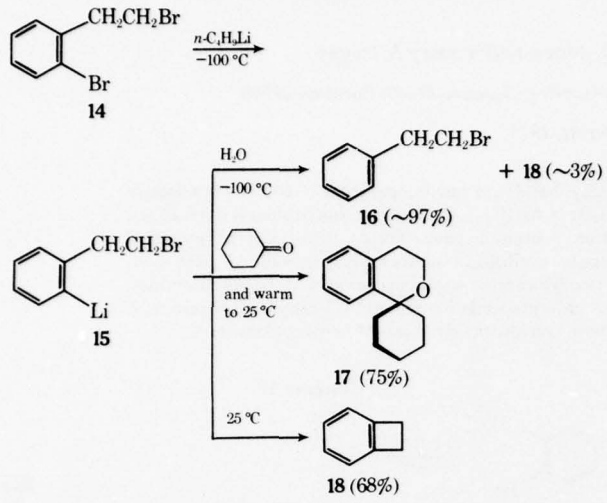
This was unexpected in view of the earlier report[3] which suggested that halogen–metal exchange occurred at the aryl halide function in a similar reaction with *p*-bromobenzyl bromide. When excess (2 equiv) of *n*-butyllithium was employed the product was bibenzyl, the product expected by complete halogen–metal exchange in **3** prior to the addition of water. Similar results were obtained with *o*-iodobenzyl iodide (**5**); however, the distribution of products (**6**, 30%; **7**, 37%) was different from that obtained with **1** when 1 equiv of *n*-butyllithium was employed.

Scheme II



***o*-Bromobenzyl Chloride (8).** Reaction of **8** follows a dramatically different course of reaction than that observed for **1**; *o*-lithiobenzyl chloride (**9**) is formed exclusively at −100 °C after approximately 5 min when 1 equiv of *n*-butyllithium is employed. *o*-Lithiobenzyl chloride is stable in solution at −100 °C and can be elaborated as shown in Scheme II: (a) by conversion to benzyl chloride (88% isolated yield) by addition of water, (b) by conversion to spiro[cyclohexane-1,1′-phthalan] (**10**, 75% isolated yield) by addition of cyclohexanone, and (c) by conversion to *N*-phenylphthalimidine (**11**, 73% isolated yield) by addition of phenyl isocyanate. Considerable effort was made to determine whether **9** might be converted to benzocyclopropene (**13**), particularly since Radlick and Crawford[4] have observed formation of benzocyclopropene by a similar process involving *o*-bromobenzyl methyl ether and *n*-butyllithium at −40 °C. Samples of **9** in the tetrahydrofuran–hexane solvent mixture were allowed to warm to room temperature prior to decomposition with water.[5] The product was pro-

Scheme III



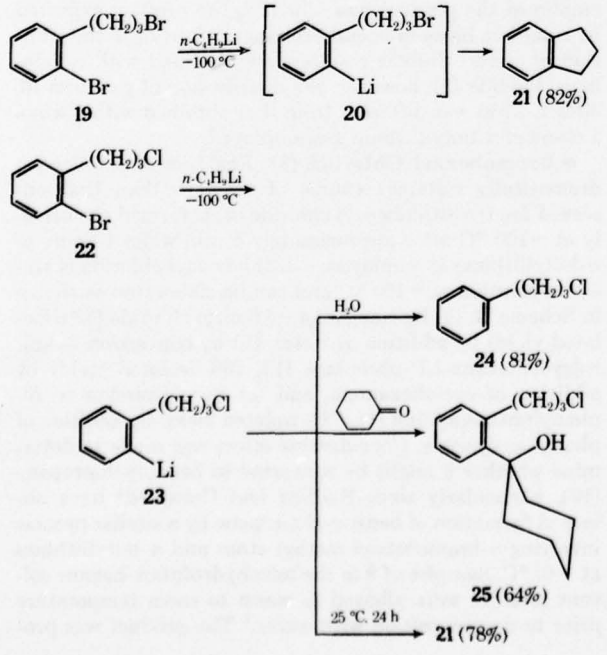
cessed at room temperature to minimize possible decomposition of **13**; however, only benzyl chloride, 9,10-dihydroanthracene (**12**, 43% isolated yield), and higher condensation products were detected. Similar results were obtained when **9** was formed in more dilute solutions of solvent.

β-(*o*-Bromophenyl)ethyl Bromide (14). Aryl halogen–metal exchange by reaction of **14** with *n*-butyllithium is selective at −100 °C; the lithio derivative **15** is formed rapidly (approximately 5 min) and can be elaborated as shown in Scheme III. The intramolecular cylization of **15**, which occurs when **15** is warmed, constitutes a new and highly efficient synthesis of benzocyclobutene[6] (**18**).

γ-(*o*-Bromophenyl)propyl Bromide (19). While one can anticipate selectivity in halogen–metal exchange similar to that described for **14** for *m*- and *p*-bromoalkyl halides, certain ortho isomers, such as **19**, present a new problem since entropy factors are favorable for intramolecular cyclization. In order to test this possibility the reactions of **19** and **22** with *n*-butyllithium at −100 °C were examined (Scheme IV). Only indan (**21**, 82% isolated yield) was detected (NMR) when **20** was formed and quenched at −100 °C with water. By contrast, γ-(*o*-lithiophenyl)propyl chloride (**23**) is formed selectively and is stable at −100 °C, and can be elaborated as shown by (a) its conversion to γ-phenylpropyl chloride (**24**, 81% isolated yield) by addition of water, and (b) by formation of **25** (64% isolated yield) by addition of cyclohexanone. When the solution containing **23** is warmed to room temperature, intramolecular cyclization occurs giving indan (**21**, 78% isolated yield).

These results suggest a broad spectrum of utility in synthesis for lithioarylalkyl halides formed at low temperature from bromoarylalkyl halides.

Scheme IV



Experimental Section

General Procedure for Halogen–Metal Exchange. Reaction of haloarylalkyl halides (0.02 mol) with *n*-butyllithium (1 molar equiv) in dry tetrahydrofuran (~130 ml)–hexane[7] (~40 ml) was carried out similar to that described for bromobenzoic acids[2a] and bromobenzonitriles.[2d] Aliquots were examined as described in ref 8.

Reaction of *o*-Bromobenzyl Bromide (1) with *n*-Butyllithium. Examination of an aliquot[8] showed complete disappearance of **1** after 30 min. The solution was stirred for a total of 1 h at −100 °C and was poured into dilute hydrochloric acid (~100 ml). The organic product, obtained from the dried ($MgSO_2$) ether extract, was essentially pure (GLC) 2-bromobibenzyl[9] (**4**, 82% yield). The analytical sample was collected by preparative GLC [20% SE-30 on Chromosorb W (60/80 mesh), 6 ft × 0.25 in., 185 °C, 90 ml/min He]: NMR ($CDCl_3$) δ 2.95 (m, 4, CH_2), 7.25 (m, 9, aromatic H).

Anal. Calcd for $C_{14}H_{13}Br$: C, 64.38; H, 5.02. Found: C, 64.17; H, 5.03.

When reaction was effected with 2 equiv of *n*-butyllithium, the only product detected was bibenzyl [**7**, 86% yield, mp 50.5–52 °C (lit.[10] mp 51.5–52.5 °C); NMR ($CDCl_3$) δ 2.95 (s, 4, CH_2), 7.25 (m, 10, aromatic H)].

Reaction of *o*-iodobenzyl bromide[11] with *n*-butyllithium was carried out as for **1**, except that the reaction mixture was stirred for 30 min at −100 °C prior to quenching with water (~75 ml) and ether (~100 ml). The dried ($MgSO_4$) organic extracts were concentrated (rotary evaporation) to afford 3.21 g of yellow oil. The crude product was distilled in vacuo to give (a) 0.57 g [37%, bp 76–86 °C (0.03 Torr)] of nearly pure (GLC, coinjection of an authentic sample) bibenzyl, and (b) 1.57 g [bp 95–110 °C (0.03 Torr)] of impure 2-iodobibenzyl. The material was obtained pure by recrystallization from a mixture (80:20) of petroleum ether[12a] and chloroform to afford 0.78 g of **6** (30%): mp 71.5–75 °C [lit.[13] bp 175 °C (0.5 Torr)]; NMR ($CDCl_3$) δ 3.10 (s, 4, CH_2), 7.25 (m, 9, aromatic H).

Anal. Calcd for $C_{14}H_{13}I$: C, 54.57; H, 4.25. Found: C, 54.48; H, 3.91.

Reactions of *o*-Bromobenzyl Chloride[14] (8). A. Conversion to Benzyl Chloride. Analysis of an aliquot[17] obtained from **8** (0.025 mol) and *n*-butyllithium (0.025 mol) at −100 °C 10 min after mixing showed (NMR) essentially only benzyl chloride. The entire mixture was added to a mixture of water (50 ml) and ether (200 ml). Benzyl chloride [88% yield, bp 177–180 °C (lit.[18] bp 179 °C)] was obtained by distillation of the dried organic extract.

B. Spiro[cyclohexane-1,1′-phthalan] (10). The above mixture prepared from **8** (0.05 mol) was treated at −100 °C with *n*-butyllithium (0.05 mol) followed by cyclohexanone (0.075 mol); the resulting mixture was allowed to warm to 25 °C and was poured into water (~100 ml). The organic material obtained from the dried ether extract was distilled in vacuo to give 7.9 g (84% yield) of **10**: bp 87–89 °C (0.01 Torr); pure by GLC; NMR ($CDCl_3$) δ 1.7 (broad s, 10, aliphatic H), 5.1 (s, 2, CH_2O), 7.2 (m, 4, aromatic H).

Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.85; H, 8.62.

C. Preparation of *N*-Phenylphthalimidine (11). Reaction was carried out as in A above; the mixture was stirred for 40 min at −105 °C, phenyl isocyanate (5.95 g, 0.05 mol) in hexane[7] (~25 ml) was added, and the reaction mixture was allowed to warm to room temperature. The entire mixture was added to water (~100 ml) and ether (~200 ml) and the dried ($MgSO_4$) organic extracts were concentrated (rotary evaporation) to afford 8.44 g of pink semisolid. The crude product was recrystallized twice from a mixture (80:20) of petroleum ether[12b] and chloroform to give 3.82 g (**11**, 73%, mp 156–158 °C, lit.[19] mp 160 °C) of nearly pure **11**. The material

was obtained pure by two successive recrystallizations; mp 166–167 °C; NMR ($CDCl_3$) δ 4.95 (s, 2, CH_2), 7.80 (m, 9, aromatic H).

Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.36; H, 5.38; N, 6.63.

D. Conversion to 9,10-Dihydroanthracene (12). The reaction was carried out as in A above; the mixture was processed by a variety of procedures to detect benzocyclopropene[4,20] (**13**, NMR[21] δ 3.11, CH_2). In a typical experiment the mixture was allowed to warm to 25 °C (~3 h); anions were decomposed by addition of water (~5 ml) and the solution was dried ($MgSO_4$, excess). In one experiment, low-boiling materials (identified by NMR spectral analysis as THF, hexane, and *n*-butyl bromide) were removed at 45 °C (150 Torr). The residue contained 9,10-dihydroanthracene and benzyl chloride in the ratio of 70:30 [NMR ($CDCl_3$) δ 3.9 and 4.5, respectively for CH_2 (singlets)]. Recrystallization of the residue from petroleum ether[12a] or ethanol gave pure 9,10-dihydroanthracene (**12**, 0.97 g, 43% yield, mp[22] and mmp 108–110 °C).

Reactions of *o*-Bromophenethyl Bromide (14). A. Phenethyl Bromide. Reactions of **14**[23] [0.03 mol, prepared in 83% yield by reaction of *o*-bromophenethyl alcohol[24] with hydrobromic acid (48%)] with *n*-butyllithium (0.03 mol) at −100 °C was complete <5 min after mixing. Analysis of aliquots[8] showed only phenethyl bromide[25] and benzocyclobutene, in the ratio of 97:3, to be present.

B. Spiro[cyclohexane-1,1′-isochroman] (17). The solution of **15** (0.03 mol), prepared as in A, above, was treated at −105 °C with cyclohexanone (0.04 mol) and the resulting mixture was allowed to warm to 20 °C. The mixture was added to water (~100 ml) and was extracted with ether. The oil obtained from the dried ($MgSO_4$) ether extract was distilled in vacuo to give pure **17**: bp 110–115 °C (0.07–0.09 Torr); NMR ($CDCl_3$) δ 1.7 (m, 10, aliphatic H), 2.9 (t, 2, $ArCH_2$), 4.05 (t, 2, CH_2O), 7.5 (m, 4, aromatic H)].

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.92; H, 9.13.

C. Benzocyclobutene (18). A solution of **15** (0.0189 mol), prepared as described in A above, was stirred for 0.5 h at −100 °C and allowed to warm to 25 °C. The resulting mixture was added to water (~100 ml) and the organic products were collected by extraction with ether. The crude product (2.67 g) was distilled to give 1.57 g of a clear, colorless oil [bp 77 °C (70 Torr)]. Spectral analysis (NMR) of the oil showed it to be a mixture of benzocyclobutene (**18**, 80%, 68% yield), tetrahydrofuran (5%), and *n*-butyl bromide (15%). Pure benzocylobutene[6] was collected by preparative GLC [20% SE-30 on Chromosorb W (60/80 mesh), 6 ft × 0.25 in., 150 °C, 90 ml/min He]: NMR ($CDCl_3$) δ 3.18 (s, 4, CH_2), 7.10 (m, 4, aromatic H); ir 1450, 1010, 775, 720 cm^{-1}; molecular ion *m/e* 104; $n^{23}D$ 1.5411 (lit.[26] $n^{25}D$ 1.5409).

Anal. Calcd for C_8H_8: C, 92.96; H, 7.74. Found: C, 92.34; H, 7.70.

Reaction of γ-(o-Bromophenyl)propyl Bromide (19) with n-Butyllithium. Formation of Indan (21). Reaction of **19** [0.025 mol, prepared from β-(*o*-bromophenyl)propanoic acid[2c] by reduction to γ-(*o*-bromophenyl)propanol (90% yield, bp 100–105° (0.02–0.01 Torr), lit.[27] bp 106–108 °C (0.5 Torr), with lithium aluminum hydride and subsequent conversion of the alcohol to **19** (81% yield, bp 104–108 °C (0.6–0.5 Torr), lit.[27] bp 84–85 °C (0.3 Torr), with hydrobromic acid (48%)] with *n*-butyllithium (1 molar equiv) at −100 °C was complete after 15 min (aliquots[28] indicated only indan). The mixture was decomposed with water (50 ml) and processed by extraction (ether) and the dried ($MgSO_4$) organic extracts were concentrated (rotary evaporation) to give a residue which was distilled in vacuo to afford 2.42 g [**21**, 82% yield, bp 176–177 °C, lit.[29] bp 177 °C (760 mm)] of pure indan: NMR ($CDCl_3$) δ 2.05 (m, 2, $-CH_2$), 2.92 (t, 4, $-CH_2$), 7.2 (m, 4, aromatic H).

Anal. Calcd for C_9H_{10}: C, 91.47; H, 8.53. Found: C, 91.52; H, 8.41.

Reactions of γ-(o-Bromophenyl)-1-propyl Chloride[30] (22). A. Conversion to 3-Chloro-1-phenylpropane (24). Studies of aliquots[28] obtained 15 min after the addition of *n*-butyllithium (1 molar equiv) to **22** (1 molar equiv) at −100 °C showed no starting material and only **24**. The entire product was added to water and the organic residue obtained from the dried ($MgSO_4$) ether extract was distilled to give pure **24** (81% yield, bp 218–220 °C, lit.[31] bp 219–220 °C).

B. Conversion to Indan (21). When the solution of **23**, prepared at −100 °C, was warmed to 20 °C (24 h) prior to addition of water, pure indan (**21**, 78% yield, bp 176–177 °C[29]) was obtained.

C. Conversion to 25. The solution of **23** (0.05 mol) prepared as in A was treated at −100 °C with cyclohexanone (2 molar equiv) at −100 to −90 °C and the resulting mixture was allowed to warm to 25 °C (24 h). The crude product (obtained by addition to water with subsequent extraction with ether) was distilled through a short Vigreux column to give cyclohexanone containing some **25** (bp <100°, 0.04 Torr). The column was replaced by a short-path column and nearly pure **25** [8.1 g, 64% yield, bp 140–145 °C (0.04 Torr)] was collected. Fractionation of this material through a short Vigreux column gave the analytical sample: bp 153–156 °C (0.03 Torr); NMR ($CDCl_3$) δ 1.8 (m, 13, aliphatic H), 3.2 (m, 2, $-CH_2$), 3.65 (t, 2, $-CH_2$), 7.35 (m, 4, aromatic H).

Anal. Calcd for $C_{15}H_{21}ClO$: C, 71.21; H, 8.37; Cl, 14.03. Found: C, 71.51; H, 8.48; Cl, 13.75.

Registry No.—**1**, 3433-80-5; **4**, 57918-64-6; **5**, 40400-13-3; **6**, 35444-96-3; **7**, 103-29-7; **8**, 578-51-8; **10**, 171-80-2; **11**, 5388-42-1; **12**, 613-31-0; **14**, 1074-15-3; **15**, 57918-65-7; **17**, 57918-66-8; **18**, 694-87-1; **19**, 1075-28-1; **21**, 496-11-7; **22**, 57918-67-9; **23**, 57918-68-0; **24**, 104-52-9; **25**, 57918-69-1; *n*-butyllithium, 109-72-8; cyclohexanone, 108-94-1; phenyl isocyanate, 103-71-9.

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(1) Supported by the U.S. Army Research Office through Grant DAHCO4 74 GD128.
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(5) In a separate experiment, the reaction mixture was quenched with water and the dried ($MgSO_4$) organic solution was concentrated in vacuo at ~20° to give a residue which contained 9,10-dihydroanthracene by GLC (coinjection of an authentic sample).
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(14) Prepared [74% yield, bp 73–74 °C (0.2 Torr), lit.[15] bp 110–111 °C (15 Torr)] from *o*-bromobenzyl alcohol[16] by reaction with thionyl chloride.
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(25) Authentic material was prepared in 83% yield by reaction of phenethyl alcohol with hydrobromic acid (48%), bp 52–54 °C (0.03 Torr) [lit.[23] bp 93–96 °C (13 Torr)].
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(30) Prepared (71% yield) from reaction of γ-(*o*-bromophenyl)propanol[27] with thionyl chloride, bp 90–94 °C (0.3–0.4 Torr). Anal. Calcd for $C_9H_{10}BrCl$: C, 46.28; H, 4.32; Br, 34.22. Found: C, 46.35; H, 4.41; Br, 34.06.
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Elaboration of Bromoarylnitriles[1]

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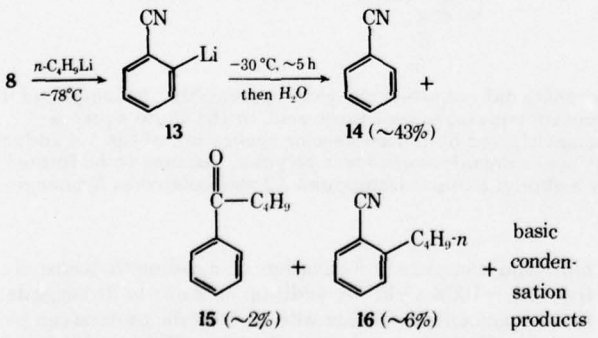
n-Butyllithium reacts selectively at −100 °C with the isomeric bromobenzonitriles by halogen–metal exchange. The resulting lithiobenzonitriles are stable at −100 °C and can be elaborated with electrophiles to give good yields of substituted benzonitriles, or, in the case of *o*-bromobenzonitrile, cyclic products derived from them. Studies of reactions of bromobenzylnitriles and bromophenylpropionitriles with *n*-butyllithium at −100 °C are also described.

The preparation of aryllithium reagents from isomeric bromobenzonitriles by halogen–metal exchange with *n*-butyllithium has been reported;[2] however, such derivatives have not been useful as synthetic intermediates. The low yields[2] of functionalized products obtained by reaction of such lithioarene intermediates with electrophiles are due, at least in part, to the reactivity of the nitrile function with organometallic reagents. The recent observation that bromine–lithium exchange can be effected selectively at −100 °C with aryl bromides containing carboxylate[3a] and, with limitations,[3b] methyl ester functions suggested that bromobenzonitriles could be efficiently elaborated at very low temperature. This has been shown to be the case.

The isomeric bromobenzonitriles were treated in tetrahydrofuran–hexane with *n*-butyllithium at −100 °C. In the case of *o*-bromobenzonitrile, essentially identical results were obtained at −78 °C; halogen–metal exchange was complete[4a] in 5 min at −100 °C. The derived lithioarene intermediates were then functionalized by addition of suitable electrophiles. The results, summarized in Table I, are self-explanatory; however, attention should be called to the fact that intramolecular cyclizations of product anions with the adjacent nitrile functions generally occurred in the ortho series.

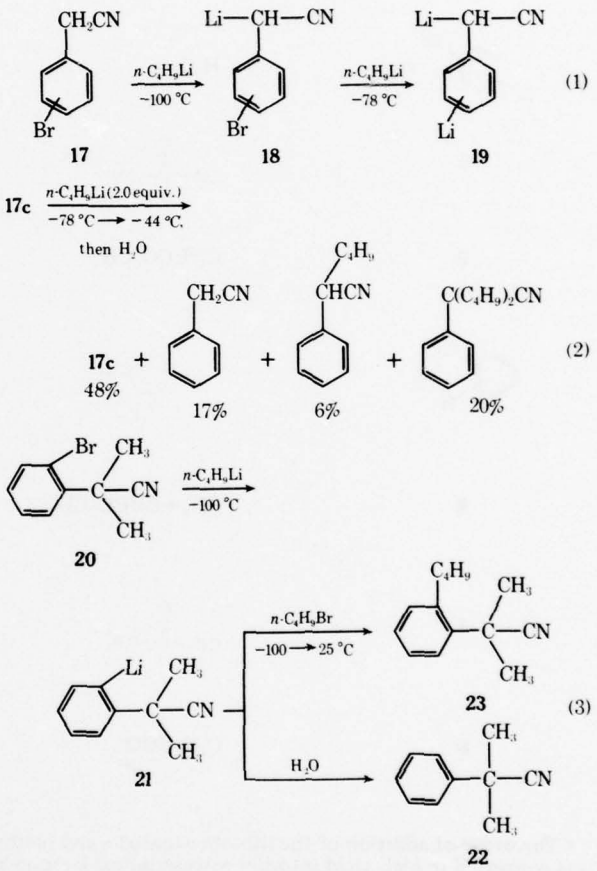
The stability of the derived lithiobenzonitriles was examined briefly by warming *o*-lithiobenzonitrile, subsequent to its formation at −78 °C, for 5 h at −30 °C prior to the addition of water. The products, shown in Scheme I,

Scheme I



suggest that (1) the lithium derivative, once formed, is reasonably stable (~43% of **14**), and (2) reaction of the lithium reagent with *n*-butyl bromide, formed during the exchange reaction, becomes significant (~6% of **16** plus butylated condensation products) at higher temperatures. The formation of significant quantities of higher molecular weight basic condensation products is assumed to result, in part, by condensation of **13** with **16** and with itself. While the mixture of condensation products was not resolved,[6] samples were hydrolyzed with hydrochloric acid and with alkali. No anthraquinone was detected in the resulting products.[7]

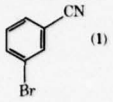
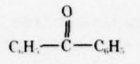
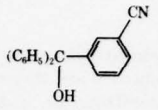
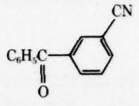
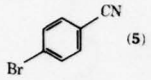
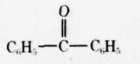
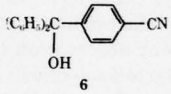
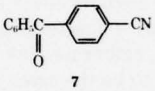
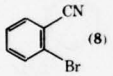
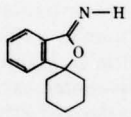
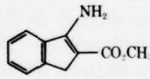
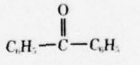
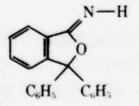
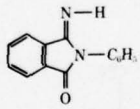
Scheme II



a. ortho
b. meta
c. para

It was of interest to determine whether or not anions derived from homologous bromobenzylnitriles would undergo halogen–metal interchange (Scheme II). Reaction of **17** with *n*-butyllithium at −100 °C gave **18**;[8] however, the anionic character of the benzylic carbon in **18** inhibited halogen–metal exchange in **18** at −100 °C with excess *n*-butyllithium. Examination of aliquots[4a] treated with water after 1 h at −100 °C obtained when excess *n*-butyllithium was employed showed ratios of benzylnitrile to unchanged bromobenzylnitrile of 3.5/97, 1/99, and 0.5/99.5 for **17a**, **17b**, and **17c**, respectively. There was no appreciable change in their ratios after an additional 2 h at −100 °C. Exchange was also slow at −78 °C (6.2, 7.2, and 5.0%, respectively for

Table I. Reaction of Isomeric Lithiobenzonitriles

Substrate	Reactant	Product	Isolated yield, %
 (1)	H_2O	 2	72
1		 3	86
1	$C_6H_5CO_2CH_3$	 4	33
 (5)	H_2O	**2**	82
5		 6	83
5	$C_6H_5CO_2CH_3$	 7	47[a]
 (8)		 9	82[b]
8	$CH_2{=}CHCO_2CH_3$	 10	9[c,d]
8		 11	50
8	C_6H_5NCO	 12	75[e]

[a] The order of addition of the lithiobenzonitrile and methyl benzoate did not affect the yield appreciably.[5] [b] Compound 9 was converted in high yield into the corresponding lactone by reaction with (a) hydrochloric acid, or (b) dilute aqueous sodium hydroxide followed by acidification. [c] Compound 10 was anticipated by intramolecular cyclization of the 1,4 adduct with subsequent enolization of the derived imino function. [d] The major organic residue was polymer, assumed to be formed from the product derived subsequent to 1,2 addition to the ester carbonyl group. [e] Compound 12 was isolated as *N*-phenylphthalimide.

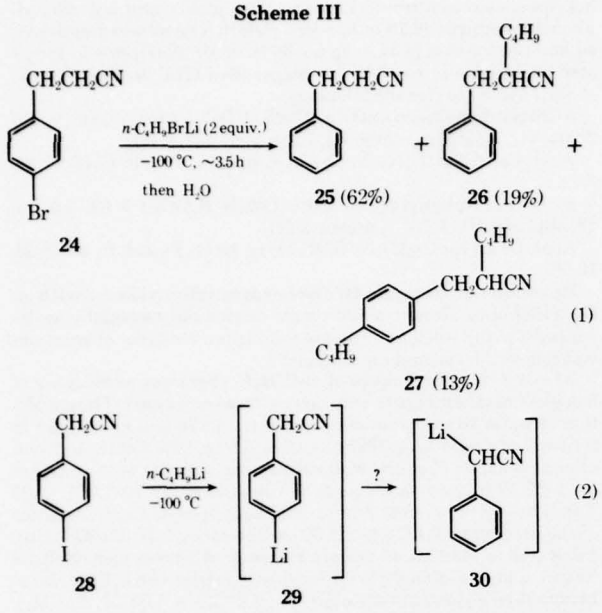
17a, 17b, and **17c** after ~4.5 h);[4a] however, some butylation occurred, presumably by reaction of **18** or **19** with *n*-butyl bromide, at −78 °C.

When reaction of **17** with *n*-butyllithium is carried out at higher temperatures (−44 °C), halogen–metal exchange is significantly increased; however, butylation of derived anions by *n*-butyl bromide, formed by exchange, becomes a significant side reaction. Thus, warming the product of reaction of **17c** with 2 equiv of *n*-butyllithium, formed at −78 °C, to −44 °C gave a product containing nitriles in the ratios shown in eq 2, together with three other components which were not examined.

When benzylic anion formation is disallowed, as in **20,** halogen–metal exchange is rapid (~100% yield after 10 min) and complete.[4a] Formation of α,α-dimethylbenzonitrile (**22,** ~100% yield) by addition of water to **21** suggests that bromobenzylic nitriles with no benzylic protons can be conveniently elaborated through the aryllithium intermediate. This was demonstrated by allowing the mixture prepared from **20** to warm to room temperature; α,α-dimethyl(*o*-butylbenzyl)nitrile (**23**) was formed by reaction of **21** with *n*-butyl bromide, formed by exchange, and was isolated pure in 74% yield.

When the alkylnitrile function in the arene is not benzylic, then halogen–metal exchange occurs readily (Scheme III). While the primary reaction of **24** with 1 equiv of *n*-butyllithium is anion formation at the methylene group adjacent to the nitrile function,[9] the anionic center is suffi-

Scheme III



ciently removed to permit complete halogen–metal exchange with the second equivalent of *n*-butyllithium. Such reactions are not, however, of synthetic interest since there are two anionic centers available for reaction with E^+. Such reactions are further complicated by the fact that appreciable butylation[10] occurs (**26** and **27**) even at −100 °C. It is also of interest to note that iodine–lithium exchange is sufficiently more rapid than bromine–lithium exchange to permit appreciable halogen–metal exchange in **28** (80%) in preference to proton removal with only 1 equiv of *n*-butyllithium (eq 2, Scheme III);[11] however, attempts to elaborate **29** and/or **30** formed from **28** and 1.5 equiv of *n*-butyllithium at −100 °C, with cyclohexanone, led to a complex unresolved mixture containing butylated products.

Experimental Section

Isomeric Bromobenzonitriles. General Procedure. Conversion of m-Bromobenzonitrile (1) to Benzonitrile (2). *m*-Bromobenzonitrile[12] (5.00 g, 0.0275 mol), tetrahydrofuran (~125 ml, freshly distilled over lithium aluminum hydride), and dry hexane[13] (~35 ml) were introduced, under nitrogen, into a three-neck flask equipped with a low-temperature thermometer, addition funnel, mechanical stirrer, and nitrogen inlet tube. The reaction mixture was cooled to −100 °C (liquid nitrogen–diethyl ether bath) and *n*-butyllithium (11.9 ml, 0.0275 mol, 2.3 M solution in hexane) was added rapidly (the rate of addition was adjusted such that the temperature did not momentarily exceed −92 °C). Examination of aliquots[4a] showed that halogen–metal exchange was complete <5 min after the addition of *n*-butyllithium (1 equiv). The reaction mixture was poured into water (~200 ml). The organic layer was separated, and the aqueous layer was extracted with three 100-ml portions of ether. The organic extracts were combined, dried ($MgSO_4$), and concentrated (rotary evaporation) to afford 3.10 g of light, yellow oil. This material was distilled to give 2.03 g [72%, bp 188–191 °C, lit.[14] bp 190.6 °C (760 mm)] of pure (GLC)[4a] benzonitrile.

Preparation of Diphenyl(*m*-cyanophenyl)carbinol (3). *Reaction of 1 (0.0275 mol) in a mixture of THF (~125 ml)–hexane*[13] (~35 ml) with *n*-C_4H_9Li (0.0275 mol) was carried out as described in the general procedure. Benzophenone (0.0275 mol) in dry THF (~30 ml) was added; the reaction mixture was warmed to 20 °C and poured into water (100 ml). The organic layer was separated and the aqueous layer was extracted once with ether (100 ml). The organic extracts were combined, dried ($MgSO_4$), and concentrated to afford 8.65 g of yellow oil. The material was recrystallized once from petroleum ether[15a] to give 6.76 g (86% mp 87–92 °C) of nearly pure **3**. Elution of a portion (400 mg) of this material on a preparative silica gel plate (fluorescent indicator) with a mixture (80:20) of petroleum ether[15c] and ether afforded pure **3** (380 mg, 82%, mp 96.5–98.5 °C); ir ν_{OH} 3330, ν_{CN} 2170 cm^{-1}.

Anal. Calcd for $C_{20}H_{15}NO$: C, 84.18; H, 5.30; N, 4.91. Found: C, 84.23; H, 5.36; N, 4.85.

Preparation of 3-Cyanobenzophenone (4). Reaction of **1** (0.0275 mol) in a mixture of THF (~125 ml)–hexane[13] (~30 ml) with *n*-C_4H_9Li was carried out as described above. The reaction mixture was stirred at −100 °C for 10 min; an aliquot (~10 ml) was quenched with water and dried ($MgSO_4$), and examination of the residue by GLC (5% SE-30 on Chromosorb W, 3 ft × 0.25 in., 105 °C, 45 ml/min He] indicated complete conversion of **1** to 3-lithiobenzonitrile.[4a] Methyl benzoate (0.029 mol) in dry THF (~25 ml) was added; the reaction mixture was warmed to 25 °C and poured into water (100 ml). Ether extraction of the aqueous layer and concentration of the organic extracts afforded 5.72 g of yellow oil. The material was recrystallized twice from methanol to give 1.7 g [33%, mp 90–92 °C (lit.[16] mp 92 °C)] of pure 3-cyanobenzophenone.

Conversion of *p*-Bromobenzonitrile (5)[12] to Benzonitrile (2). Reaction of **5** (0.0275 mol) in a mixture of dry THF (~125 ml)–hexane[13] (~35 ml) with *n*-C_4H_9Li (0.0275 mol) and subsequent decomposition of *p*-lithiobenzonitrile with water was carried out as described for **1**. Distillation of the residue (3.02 g) gave 2.33 g (82%) of pure (GLC)[4a] benzonitrile.

Preparation of Diphenyl(*p*-cyanophenyl)carbinol (6). The procedure, starting with **5**, was essentially identical with that described for **3**. The crude product was crystallized from a mixture (85:15) of petroleum ether[15b] and chloroform to give 6.54 g (83% yield, mp 90–93 °C) of nearly pure **6** (mp 92–93.5 °C; ir (KBr) ν_{OH} 3300, ν_{CN} 2200 cm^{-1}).

Anal. Calcd for $C_{20}H_{15}NO$: C, 84.18; H, 5.30; N, 4.91. Found: C, 83.97; H, 5.31; N, 4.80.

Preparation of 4-Cyanobenzophenone (7). The procedure, starting with **5**, was essentially identical with that described for **4**. One recrystallization of the crude product from methanol gave pure **7** (mp 115–116 °C, lit.[17] mp 107–108 °C).

Anal. Calcd for $C_{14}H_9NO$: C, 81.14; H, 4.38; N, 6.76. Found: C, 81.43; H, 4.41; N, 6.66.

Conversion of *o*-Bromobenzonitrile (8)[12] to Phthalan 9. Reaction of **8** (0.0275 mol) in THF (~125 ml)–hexane[13] (~40 ml) mixture with *n*-C_4H_9Li (0.0275 mol) was carried out as described in the general procedure, except that the reaction mixture was maintained at −78 °C (dry ice–acetone bath). Examination (GLC)[4a] of an aliquot (~10 ml) indicated only *o*-lithiobenzonitrile. Cyclohexanone (0.0296 mol) in THF (~20 ml) was added; the reaction mixture was warmed to 5 °C and was poured into ice-cold water (100 ml). Rapid extraction (chloroform) of the aqueous layer, followed by concentration of the organic extracts, gave 6.97 g of yellow oil. The crude product was distilled in vacuo to afford 4.5 g [82%, bp 104–105 °C (0.03 Torr)] of pure iminophthalan **9**: ir ν 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.8 (broad s, 10 aliphatic H), 6.75 (broad s, 1, NH), 7.4 (m, 3, aromatic H), 7.85 (m, 1, aromatic H).

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.39; H, 7.35; N, 6.88.

Acid (concentrated hydrochloric) or base (10% sodium hydroxide) hydrolysis of phthalan **9** gave the corresponding known lactone[18] (mp, mmp 80–82 °C) in high yield.

Preparation of 2-Carbomethoxy-3-aminoindene (10). Reaction of **8** (0.0275 mol) in a THF (~125 ml)–hexane[13] (~40 ml) mixture with *n*-C_4H_9Li (0.0275 mol) was carried out as described above. Methyl acrylate[19] (0.030 mol) in dry hexane[13] (~25 ml) was added; the reaction mixture was warmed to 0 °C and poured into water (~100 ml). The crude product was distilled in vacuo to afford 1.47 g of yellow oil. The oil was recrystallized once from petroleum ether[15a] to give 0.45 g (9%, mp 103.5–105 °C) of pure **10**: NMR ($CDCl_3$) δ 3.62 (s, 2, benzylic H), 3.90 (s, 3, $-OCH_3$), 6.0 (broad s, 2, $-NH_2$), 7.5 (m, 4, aromatic H).

Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 70.09; H, 5.63; N, 7.30.

The distillation residue appeared to be polymeric.

Preparation of Phthalan 11. Reaction of **8** (0.0275 mol) in a THF (~125 ml)–hexane[13] (~35 ml) mixture with *n*-C_4H_9Li (0.0275 mol) was carried out as described in the general procedure. Benzophenone (0.028 mol) in THF (~25 ml) was added, and the reaction mixture was warmed to 0 °C and poured into cold water (~100 ml). Rapid extraction (ether) of the aqueous layer and concentration (rotary evaporation) of the organic extracts afforded 8.38 g of yellow solid. The crude product was recrystallized from petroleum ether[15a] to give 3.93 g (50%, mp 106–107.5 °C) of nearly pure iminophthalan **11**. One further recrystallization of this material gave the pure product, 2.56 g (33%, mp 108.5–109.5 °C); ir ν 1660 cm^{-1}.

Anal. Calcd for C_9H_8BrN: C, 51.45; H, 3.84; N, 6.67. Found: C, 51.31; H, 3.88; N, 6.70.

Preparation of *N*-Phenylphthalimide (12). Reaction of 8 (0.275 mol) in a THF (~125 ml)–hexane[13] (~35 ml) mixture with n-C_4H_9Li (0.0275 mol) was carried out as described above, except that the reaction mixture was maintained at −78 °C. Phenyl isocyanate (0.03 mol) was added; the reaction mixture was warmed to 25 °C and poured into dilute aqueous hydrochloric acid (5% ~150 ml) and the resulting mixture was allowed to stand for 2 h. Extraction (chloroform) of the aqueous layer and concentration of the organic extracts afforded 6.19 g of yellow semisolid. The crude product was recrystallized once from a mixture (85:15) of absolute alcohol and chloroform to give 4.6 g (75%, mp 206–210 °, lit.[20] mp 208 °C) of **12.**

Reaction of *o*-Bromobenzonitrile and *n*-Butyllithium at −30 °C. The reaction mixture, prepared as described in the general procedure using 1 equiv of n-C_4H_9Li at −78 °C, was allowed to warm to ~−30 °C and was maintained at this temperature for 5 h. The resulting product was added to cold concentrated hydrochloric acid (~200 ml) and separated into neutral and basic components by conventional methods. The isolated neutral component was analyzed by GLC [20% SE-30 on Chromosorb W (60/80 mesh), 6 ft × 0.25 in., 180 °C, 80 ml/min He; the components were identified by coinjection of authentic materials and/or by isolation] and was found to contain benzonitrile (1.13 min, ~43% yield), o-butylbenzonitrile [**16,** ~6% yield, 2.94 min; NMR ($CDCl_3$) δ 0.95 (t, 3, CH_3), 1.5 (m, 4, CH_2), 2.85 (t, 2, ArCH_2), 7.4 (m, 4, aromatic H); ir ν_{CN} 2200 cm^{-1}] and valerophenone [**15,** ~4% yield, 3.13 min; NMR ($CDCl_3$) δ 0.7–1.95 (m, 6, aliphatic H), 3.0 (t, 2, ArCH_2), 7.45 (m, 3, aromatic H), 8.00 (m, 2, aromatic H)]. The dark green solid (1.74 g) obtained by neutralization of the acidic fraction was multicomponent; attempts (recrystallization, TLC) to resolve this mixture into pure components were unsuccessful. Hydrolysis of the presumed imino functions with both ethanolic potassium hydroxide–water and with dilute hydrochloric acids gave mixtures (five colored bands on TLC); however, TLC experiments showed that no anthraquinone was present.

Preparation of the Isomeric Bromobenzylnitriles. o-Bromobenzylnitrile[21] [**17a,** NMR ($CDCl_3$) δ 3.82 (s, 2, CH_2)], m-bromobenzylnitrile[21] [**17b,** NMR ($CDCl_3$) δ 3.82 (s, 2, CH_2)], and p-bromobenzylnitrile[21] [**17c,** NMR ($CDCl_3$) δ 3.70 (s, 2, CH_2)] were prepared in good yield by conventional procedures from the corresponding bromobenzyl bromides. The bromobenzyl bromides were prepared from the corresponding bromotoluenes by bromination with N-bromosuccinimide[22] or from the corresponding bromobenzyl alcohol[23a] by reaction with aqueous hydrobromic acid (48%).[23b] The latter process was preferable since the nitriles obtained were free of trace impurities as determined by NMR and GLC analysis.

α,α-Dimethyl-*o*-bromobenzylnitrile (20). o-Bromobenzonitrile (**17a,** 20.0 g, 0.103 mol) dissolved in dimethylformamide (40 ml) was added slowly, under nitrogen, to a mixture of sodium hydride (5.2 g, 0.12 mol), dimethylformamide (40 ml), and benzene (20 ml) at 0 °C. The mixture was stirred for 0.5 h at 0 °C and methyl iodide (17 g, 0.12 mol) was added slowly. The resulting mixture was warmed to 25 °C (~0.5 h) and poured into water (100 ml) and the aqueous layer was extracted with four 60-ml portions of chloroform. The oil [bp 103 °C (0.2 Torr)] obtained from the dried chloroform was dissolved in dimethylformamide (40 ml) and re-treated, as above, with sodium hydride and methyl iodide. The oil, obtained as described above, was distilled to give pure **20** [19.5 g, 87% yield; bp 95–105 °C (~0.03 Torr); NMR ($CDCl_3$) δ 1.9 (s, 6, CH_3), 7.4 (m, 4, aromatic H)].

Anal. Calcd for $C_{10}H_{10}BrN$: C, 53.60; H, 4.50; Br, 35.66; N, 6.25. Found: C, 53.43; H, 4.37; Br, 35.53; N, 6.15.

α-Butylphenylacetonitrile and α,α-Dibutylphenylacetonitrile. n-Butyllithium (13.3 ml, 0.032 mol, 2.4 M solution in hexane) was added dropwise to a cold (−78 °C, dry ice–acetone bath), stirred solution of phenylacetonitrile (7.5 g, 0.064 mol) in THF (100 ml, freshly distilled from lithium aluminum hydride) under an atmosphere of nitrogen. n-Butyl bromide (3.44 ml, 0.032 mol) was added rapidly. The mixture was warmed to 0 °C (5 min) and cooled to −78 °C, and the treatment with n-butyllithium and n-butyl bromide was repeated; the resulting mixture was warmed to room temperature and stirred for 7 h. The mixture was poured into water (60 ml) and the organic layer was collected in ether. Analysis of the oil (11.2 g) obtained from the dry ($MgSO_4$) ether extract by GLC [20% SE-30 on Chromosorb W (60/80 mesh), 6 ft × 0.25 in., 230 °C, 70 ml/min He] indicated three components in the ratio of 74:21:5 [phenylacetonitrile (1.31 min, ~7.5% yield), α-butylphenylacetonitrile (3.12 min, ~75% yield), and α,α-dibutylphenylacetonitrile (6.19 min, ~16% yield)]. The oil was fractionated and the fraction [6.54 g, bp 83–86 °C (0.07 Torr)] rich in butylated material was resolved by preparative GLC (column as described above) to give the following.

α-Butylphenylacetonitrile [NMR ($CDCl_3$) δ 0.6–2.0 (m, 9, aliphatic H), 3.7 (t, 1, methine H), 7.3 (s, 5, aromatic H)].

Anal. Calcd for $C_{12}H_{15}N$: C, 83.19; H, 8.73. Found: C, 83.27; H, 8.19.

α,α-Dibutylphenylacetonitrile [NMR ($CDCl_3$) δ 0.6–2.0 (m, 18, aliphatic H), 7.3 (s, 5, aromatic H)].

Anal. Calcd for $C_{16}H_{23}N$: C, 83.79; H, 10.11. Found: C, 83.88; H, 10.06.

Reactions of Isomeric Bromobenzylnitriles (17a–c) with *n*-Butyllithium. These reactions were carried out essentially as described for the isomeric bromobenzonitriles. Progress of reactions was followed by examining aliquots.[4a]

At −100 °C with 1 equiv of n-C_4H_9Li there was no evidence of halogen–metal exchange; only anions **18** were formed. Thus, addition of water to the product obtained from **17a** (5.0 g) resulted in recovery of only o-bromobenzylnitrile (4.52 g, 92% yield). Addition of methyl iodide (1 equiv) with subsequent warming of the mixture to 25 °C (2 h) gave, subsequent to distillation [bp 70–72 °C (0.05 Torr)] nearly pure (79%) 2-(o-bromophenyl)propionitrile. Analysis of the product by GLC [5% SE-30 on Chromosorb W (60/80 mesh), 3 ft × 0.25 in., 140 °C, 45 ml/min He] showed o-bromobenzylnitrile (trace) and α,α-dimethyl-o-bromobenzylnitrile (5%). Pure **2-(*o*-bromophenyl)propionitrile** [NMR ($CDCl_3$) δ 1.59 (d, 3, CH_3), 1.39 (q, 1, CH), 7.35 (m, 2, aromatic H), 7.65 (m, 2, aromatic H)] was collected by preparative GLC [20% SE-30 on Chromosorb W (60/80 mesh), 6 ft × 0.25 in., 170 °C, ~90 ml/min He].

Anal. Calcd for C_9H_8BrN: C, 51.46; H, 3.84; N, 6.66. Found: C, 51.40; H, 4.02; N, 6.63.

Reaction of 17 with 2 Equiv of n-C_4H_9Li. Results at −100 and −78 °C are described in the discussion. At higher temperatures extensive butylation of derived anions resulted. Examination of the product obtained by reaction of p-bromobenzylnitrile with n-butyllithium (2 equiv; initial reaction at −78 °C, then aged 90 min at −53 °C and 30 min at −44 °C) by GLC [5% SE-30 on Chromosorb W (60/80 mesh), 3 ft × 0.25 in., 130 °C, 45 ml/min He] obtained subsequent to the addition of water showed at least seven components. Four of these, together with their ratio, were identified by NMR and by coinjection of authentic samples (see eq 2, Scheme II, in the discussion).

Reaction of α,α-Dimethyl-*o*-bromobenzylnitrile (20) with n-C_4H_9Li. The reaction was carried out at −100 °C as described for **1.** Examination of aliquots (GLC) showed that halogen–metal exchange was complete in <10 min [the product obtained subsequent to addition of water was essentially pure α,α-dimethylbenzylnitrile (**22,** 100% yield)].[24] The solution was allowed to warm to room temperature and was stirred at 25 °C for 0.5 h prior to quenching with water. The oil, obtained in the usual way from the reaction mixture, was distilled to give essentially pure α,α-dimethyl-o-butylbenzylnitrile **(23):** bp 79 °C (0.02 Torr); molecular ion m/e 201; ir ν_{CN} 2200 cm^{-1}; NMR ($CDCl_3$) δ 0.85–1.75 (m, 7, aliphatic H), 1.65 (s, 6, CH_3), 2.15 (m, 2, CH_2), 7.95 (m, 4, aromatic H). The sample submitted for analysis was collected by GLC [20% SE-30 on Chromosorb W (60/80 mesh), 6 ft × 0.25 in., 180 °C, 70 ml/min He].

Anal. Calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51. Found: C, 83.76; H, 9.66.

β-(*p*-Bromophenyl)propionamide was prepared from β-(p-bromophenyl)propionic acid[26] in a conventional way with thionyl chloride followed by ammonium hydroxide (85%, mp 138.5–141.5 °C). An analytical sample was obtained pure by recrystallization from a mixture (80:20) of petroleum ether[15a] and chloroform, mp 147–148 °C.

Anal. Calcd for $C_9H_{10}BrNO$: C, 47.39; H, 4.42; N, 6.14; Br, 35.04. Found: C, 47.11; H, 4.40; N, 6.14; Br, 35.22.

β-(*p*-Bromophenyl)propionitrile (24) was prepared from the corresponding amide by dehydration with thionyl chloride [7 h reflux, 84% yield, bp 116 °C (0.05 Torr)].

Anal. Calcd for C_9H_8BrN: C, 51.45; H, 3.84; N, 6.67. Found: C, 51.31; H, 3.88; N, 6.70.

Reaction of β-(*p*-Bromophenyl)propionitrile (24) with n-C_4H_9Li. The reaction was carried out at −100 °C as described for **1.** Aliquots were decomposed with water and the products were analyzed by GLC [20% SE-30 on Chromosorb W (60/80 mesh), 6 ft × 0.25 in., 195 °C, 90 ml/min He]. With ~1 equiv of n-C_4H_9Li, the

ratio of **25/24** was 17/83 after 15 min; the ratio did not change after an additional 40 min at −100 °C. An additional 1.1 equiv of *n*-butyllithium was added. After 15 min the above ratio was 75/16; compound **26** was also detected. The mixture was continually stirred at −100 °C; examination of aliquots showed that the amount of **24** decreased while the amount of butylated products (**26** and **27**) increased. The mixture was quenched with water after a total of 4 h after the second addition of n-C_4H_9Li. The mixture of products obtained contained phenylpropionitrile (**25**, 62%), α-butyl-β-phenylpropionitrile (**26**, 19%), α-butyl-β-(*p*-butylphenyl)propionitrile (**27**, 13%), and an unidentified product. Products were collected by preparative GLC.

α-Butyl-β-phenylpropionitrile (26): NMR ($CDCl_3$) δ 0.9 (t, 3, aliphatic H), 1.55 (m, 6, aliphatic H), 2.9 (m, 3, aliphatic H), 7.3 (m, 5, aromatic H).

Anal. Calcd for $C_{13}H_{17}N$: C, 83.37, H, 9.15; N, 7.48. Found: C, 83.55; H, 9.05; N, 7.55.

α-Butyl-β-(*p*-butylphenyl)propionitrile (27): NMR ($CDCl_3$) δ 0.70–1.9 (m, 16, aliphatic H), 2.2 (m, 2, CH_2), 2.85 (m, 3, aliphatic H), 7.2 (m, 4, aromatic H).

Anal. Calcd for $C_{17}H_{25}N$: C, 83.89; H, 10.35. Found: C, 83.79; H, 10.60.

***p*-Iodobenzylnitrile (28).** Examination[4b] of an aliquot, quenched with water taken after 15 min from reaction of **28**[27] with 1 equiv of n-C_4H_9Li at −100 °C, showed the ratio of benzylnitrile to starting material (**28**) to be 80/20; starting material immediately disappeared upon addition of an additional 0.5 equiv of n-C_4H_9Li. Attempts to trap the anionic products from the reaction mixture with cyclohexanone gave a multicomponent mixture (GLC) which was not resolved.

Registry No.—**1**, 6952-59-6; **2**, 100-47-0; **3**, 57775-02-7; **4**, 6136-62-5; **5**, 623-00-7; **6**, 57808-43-2; **7**, 1503-49-7; **8**, 2042-37-7; **9**, 57775-03-8; **10**, 28873-85-0; **11**, 57775-04-9; **12**, 34446-14-5; **15**, 1009-14-9; **16**, 57775-05-0; **17a**, 19472-74-3; **17b**, 31938-07,5; **17c**, 16532-79-9; **20**, 57775-06-1; **23**, 57775-07-2; **24**, 57775-08-3; **26**, 54321-42-5; **27**, 57775-09-4; **28**, 51628-12-7; n-butyllithium, 109-72-8; benzophenone, 119-61-9; methyl benzoate, 93-58-3; cyclohexanone, 108-94-1; methyl acrylate, 96-33-3; phenyl isocyanate, 103-71-9; phenylacetonitrile, 140-29-4; n-butyl bromide, 109-65-9; α-butylphenylacetonitrile, 3508-98-3; α,α-dibutylphenylacetonitrile, 3508-99-4; 2-(*o*-bromophenyl)propionitrile, 57775-10-7; β-(*p*-bromophenyl)propionamide, 57775-11-8; β-(*p*-bromophenyl)propionic acid, 1643-30-7.

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(4) The degree of metalation was determined by treating aliquots with water and analyzing the dried organic products by (a) GLC [20% SE-30 on Chromosorb W (60/80 mesh), 6 ft × 0.25 in., or 5% SE-30 on Chromosorb W (60/80 mesh), 3 ft × 0.25 in., including injection of authentic starting halides and reduced products], (b) NMR, the benzylic protons of *p*-iodobenzyl nitrile and benzyl nitrile appear as sharp singlets at δ 3.75 and 3.65, respectively.
(5) Dr. Robert Piccirilli, Duke University, private communication.
(6) Thin layer chromatography showed it to be multicomponent.
(7) Imino anthraquinones (or *N*-butyl derivatives) were anticipated as possible products of self-condensation of **13** by analogy to products of self-condensation of lithium *o*-lithiobenzoates (cf. ref 3b).
(8) Reaction of **18a**, formed from **17a** and 1 equiv of *n*-butyllithium, with methyl iodide, gave a 79% yield of nearly pure 2-(*o*-bromophenyl)propionitrile (see Experimental Section).
(9) Analysis of the organic products obtained by decomposition of aliquots with water showed 17% halogen–metal exchange after 0.5 h with 1 equiv of *n*-butyllithium.
(10) Butylation is assumed to occur by reaction of *n*-butyl bromide, formed by exchange, with the dilithio derivative formed from **24**.
(11) Studies of aliquots showed that 80% iodine–lithium exchange occurs when **28** is treated with 1 equiv of *n*-butyllithium.
(12) *o*-, *m*-, and *p*-bromobenzonitrile are commercially available.
(13) Practical grade stored over molecular sieves.
(14) G. W. A. Kahlbaum and G. von Wirkner, *Ber.*, **27**, 1894 (1894).
(15) (a) bp 90–110 °C; (b) bp 60–90 °C; (c) bp 30–60 °C.
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(24) Shown by coinjection of an authentic sample prepared from benzyl nitrile (1 equiv), sodium hydride (2 equiv), and methyl iodide (2 equiv) in dimethylformamide; bp 226 °C (754 mm); $n^{25}D$ 1.5016 (lit.[25] bp 232 °C; nD 1.50665).
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Preparation of Aroylbenzoic Acid. Reaction of Aryllithium Reagents with Phthalic Anhydride[1]

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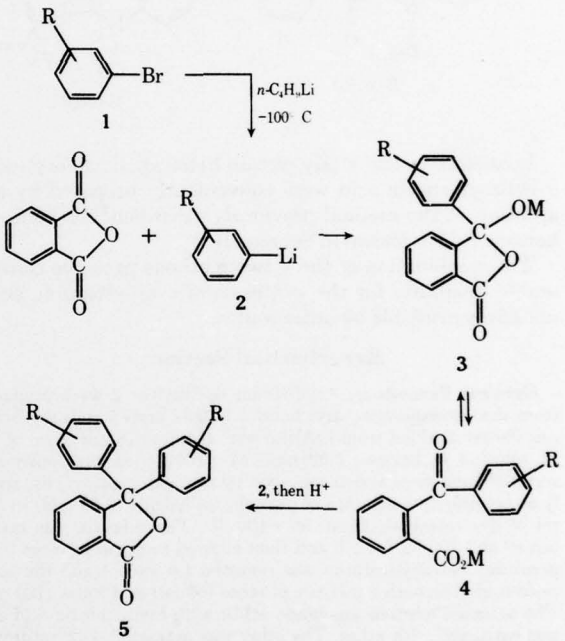
The preparation of a benzoylbenzoic acid by reaction of Grignard reagents with phthalic anhydride[2-4] offers advantages over the usual synthesis involving phthalic anhydride, aromatic hydrocarbons, and aluminum chloride in that isomers can be obviated when substituted aromatic compounds are employed. The method is limited, however, since Grignard reagents cannot be employed if the aromatic system contains functional groups that react with Grignard reagents. Since it has been shown[5-8] that organolithium reagents can be prepared at low temperature by halogen–metal exchange of aryl bromides substituted with groups normally reactive toward Grignard reagents (COO^-, CN, NO_2), the reaction of aryllithium reagents with phthalic anhydride has been examined as a route to *o*-benzoylbenzoic acids substituted with cyano functions. Previously, there has been little work related to the reaction of aryllithium with phthalic anhydride. Wittig and Leo report[9] that the reaction of phenyllithium with phthalic anhydride gives only a resinous compound and triphenylcarbinol, while Wilson reported an unworkable oil from which some diphenylphthalide[10] was isolated by distillation.

The reaction of organometallic reagents with phthalic anhydride is thought to proceed as shown in Scheme I. The products are generally *o*-benzoylbenzoic acids (**4**) and/or phthalides (**5**). Initially it was hoped that at low temperature, the equilibrium between the lithium salts **3** and **4** might favor **3**, which would obviate the necessity of employing inverse addition and/or an excess of phthalic anhydride to minimize phthalide (**5**) formation.[3] However, preliminary experiments using phenyllithium showed that this was not the case. When phthalic anhydride (1 equiv) was added to phenyllithium (1 equiv) at −78 °C the yield of phthalide **5a** was 78% base on phenyllithium. When the same ratios were maintained but the order of addition reversed, the yield of isolated phthalide **5a** was 9% while the yield of *o*-benzoylbenzoic acid was 35%. Furthermore, the yield of *o*-benzoylbenzoic acid was further increased (55%) when excess (2 equiv) of phthalic anhydride was employed.

In subsequent experiments, the aryllithium reagent was added rapidly to 2 equiv of phthalic anhydride in tetrahydrofuran at −100 °C. Reasonably good yields of substituted benzoylbenzoic acids were obtained; the results are summarized in Table I.

Scheme I



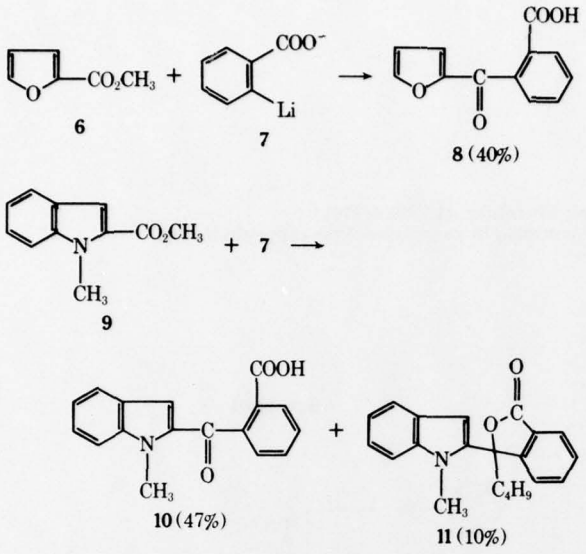
a, R = H
b, R = OCH_3 (ortho)
c, R = CN (ortho)
d, R = CN (meta)
e, R = CN (para)
f, R = NO_2 (ortho)

Table I. Reactions of Aryllithium Derivatives with Phthalic Anhydride

Aryl halide	Product[f]	Yield, %	Mp, °C
o-$CH_3OC_6H_4Br$ (**1b**)	**4b** (M = H)	70	142–144[a]
o-NCC_6H_4Br (**1c**)	**4c** (M = H)	87	146–147[b]
m-NCC_6H_4Br (**1d**)	**4d** (M = H)	60	175–176[c]
p-NCC_6H_4Br (**1e**)	**4e** (M = H)	71	179–186[d]
o-$O_2NC_6H_4Br$ (**1f**)	**4f** (M = H)	43	174–176[e]

[a] Lit.[4] 145–146 °C from CH_3COOH. [b] From H_2O. [c] From ethanol. [d] From ethanol–water. [e] From $CHCl_3$. [f] Satisfactory analytical data (±0.3% for C, H, N) for all new compounds were submitted for review.

Scheme II



Incidental to this study certain heterocyclic analogues of *o*-benzoylbenzoic acid were conveniently prepared by adaptation of the method previously described[7] for benzoylbenzoic acid as shown in Scheme II.[11]

The combination of these two methods provides considerable flexibility for the synthesis of *o*-aroylbenzoic acids not easily available by other routes.

Experimental Section

General Procedure. Aryllithium derivatives **2** were prepared from the corresponding aryl halides **1** (0.02 mol) in tetrahydrofuran (80 ml distilled from $LiAlH_4$) with *n*-butyllithium (9 ml of 2.3 M solution in hexane, 0.02 mol) at −100 °C as previously described[6,7] and were added (pumped by nitrogen pressure) as rapidly as possible to a solution of phthalic anhydride (0.04 mol) in 125 ml of dry tetrahydrofuran at −100 °C. The mixture was maintained at −100 °C for 1 h and then allowed to warm to room temperature. Tetrahydrofuran was removed (in vacuo) and the solid residue shaken with a mixture of ether (60 ml) and water (100 ml). The aqueous solution was made acidic with hydrochloric acid and was extracted with ether. The ether was extracted with saturated sodium bicarbonate to remove acid. Phthalides **5** were obtained from the ether layer. The alkaline extract was acidified and the solid was collected and recrystallized as described in Table I.

2-(2-Furoyl)benzoic acid (8) was prepared from lithium *o*-lithiobenzoate (from 0.05 mol of *o*-bromobenzoic acid) as described[6] and 2-methylfuroate. After warming the mixture to room temperature, the tetrahydrofuran was removed in vacuo and water (250 ml) was added to the residue. The aqueous solution was washed with ether, acidified with hydrochloric acid, and extracted with ether (3 × 30 ml). The dried ($MgSO_4$) ether extracts were evaporated in vacuo to give the crude acid as an oil which crystallized when treated with ethyl acetate followed by evaporation of all solvent (5.5 g, 52% yield, mp 150–153 °C, mp 154–156 °C from ethyl acetate); νC=O 1660, 1700 cm^{-1}.

Anal. Calcd for $C_{12}H_8O_4$: C, 66.67; H, 3.73. Found: C, 66.50; H, 3.95.

2-(1-Methyl-2-indoloyl)benzoic acid (10) was prepared from methyl 1-methylindole-2-carboxylate (0.03 mol) essentially as described for **8**. Tetrahydrofuran was removed from the crude reaction mixture in vacuo and water (250 ml) was added to the residue. The resulting mixture was extracted with ether. From the ether extract there was obtained 0.38 g (7%) of starting ester. The mixture of acids obtained by acidification of the alkaline layer was collected (ether extraction) and recrystallized from benzene to give 4.00 g (47% yield) of pure 2-(1-methyl-2-indoloyl)benzoic acid (**10**), mp 164–165 °C.

Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.10; H, 4.69; N, 5.01. Found: C, 72.97; H, 4.62; N, 4.91.

Evaporation of the benzene from which **10** was crystallized gave a semisolid to which some cold ether was added. The resulting solid was collected and recrystallized from ethyl acetate to give 0.88 g (mp 131–132 °C 10% yield) of lactone **11**.

Anal. Calcd for $C_{21}H_{21}NO_2$: C, 78.96; H, 6.62; N, 4.38. Found: C, 78.93; H, 6.50; N, 4.34.

Registry No.—**1b,** 578-57-4; **1c,** 2042-37-7; **1d,** 6952-59-6; **1e,** 623-00-7; **1f,** 577-19-5; **4b,** 1151-04-8; **4c,** 57901-51-6; **4d,** 57901-52-7; **4e,** 20643-60-1; **4f,** 57901-53-8; **6,** 611-13-2; **8,** 57901-54-9; **9,** 37493-34-8; **10,** 57901-55-0; **11,** 57901-56-1; phthalic anhydride, 85-44-9; lithium *o*-lithiobenzoate, 57901-57-2.

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(11) Lactone **11** is assumed to have been formed as a consequence of the slight excess of *n*-butyllithium used for preparation of **7** from *o*-bromobenzoic acid. Analogous products have been reported (see ref 7).

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Halogen–Metal Exchange in Esters of Haloaryl Acids[1]

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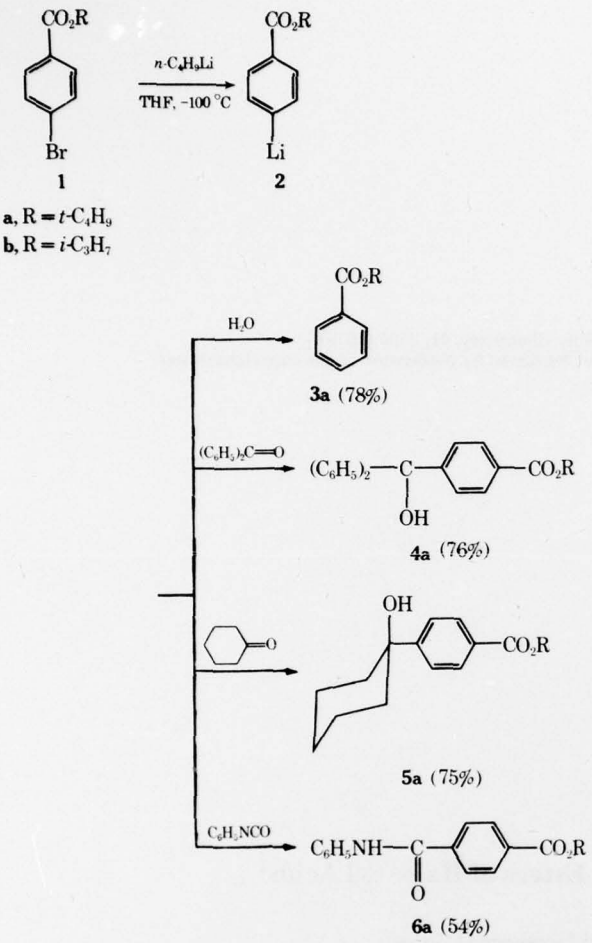
n-Butyllithium reacts selectively at −100 °C in THF–hexane with *tert*-butyl *p*-bromobenzoate by halogen–metal exchange; the resulting *tert*-butyl *p*-lithiobenzoate is stable at −100 °C and can be elaborated in high yield to give para-substituted *tert*-butylbenzoates by reactions with electrophiles. The less hindered isopropyl esters are not stable to aryllithium at −100 °C unless further hindered by ortho substitution.

Considerable progress has been made recently in developing improved procedures for the elaboration of aromatic acids utilizing derived aryllithium reagents. The method of Meyers[2] involving direct ortho metalation of oxazolines derived from aromatic acids would appear to be the method of choice for symmetrically substituted 2-aryloxazolines, since the ortho-substituted aryl halide corresponding to the position of lithiation is not a required intermediate as in halogen–metal exchange reactions. The alternative procedure,[3a] developed in our laboratory, involving direct halogen–metal exchange of the lithium salts of bromoarylcarboxylic acids at very low temperature (−100 °C) affords good yields of elaborated acids, subsequent to reaction with E^+. In addition, the process is positionally selective at the site occupied by bromine in the starting acid and is applicable to *o*-, *m*-, or *p*-bromobenzoic acids, as is the complementary procedure employing oxazolines to mask carboxyl functions to Grignard reagents.[4]

It has been shown that stable aryllithium reagents can be prepared at −100 °C with a variety of aryl bromides containing reactive functional groups (COO^-,[3] CN,[5] CH_2Cl,[6] CH_2CH_2Br,[6] *o*-NO_2[7]); however, similar reactions[8] with aryl halides containing methyl ester functions are of limited synthetic utility since the derived aryllithium reagents either self-condense or react with unchanged bromoaryl ester at low temperature (−78 → −100 °C) to give high yields of methyl benzoylbenzoates. In order to further define the limitations for synthetic reactions of aryllithium reagents containing ester functions, we have examined, as model compounds, halogen–metal exchange with *tert*-butyl *p*-bromobenzoate, isopropyl p-bromobenzoate, and isopropyl *o*-bromobenzoate. In all cases, progress of halogen–metal exchange was followed by quenching aliquots with water and determining (by NMR, GLC, and isolation of products) the ratio of starting bromoaryl ester to ester derived by replacing bromine with hydrogen.

While reaction of *tert*-butyl *p*-bromobenzoate (**1a**)[9] with *n*-propyllithium in ether at −40 °C is reported to involve preferential addition of alkyllithium to the ester function, the reaction of **1a** with *n*-butyllithium in THF–hexane at −100 °C involves selective halogen–metal exchange to give only **2a**. Reaction was complete after 5 min at −100 °C, and good yields (isolated) of elaborated aryl esters were obtained by reaction of **2a** with suitable electrophiles as shown in Scheme I.

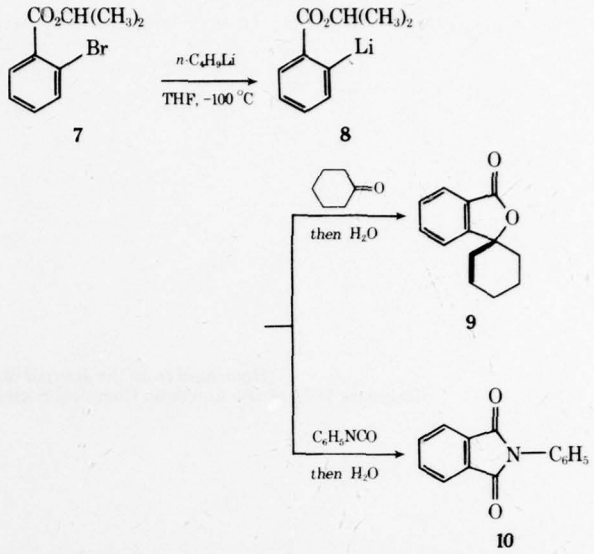
Scheme I



While **2a** is stable (during 2-h period examined) at −100 °C, some loss to condensation products was observed when the solution containing **2a** was warmed to −78 °C (1 h); extensive reaction occurred to give an unresolved multicomponent mixture (TLC) of presumably higher condensation products when the solution containing **2a** was warmed to −20 °C.

Reaction of the less hindered ester isopropyl *p*-bromobenzoate (**1b**), under similar conditions with *n*-butyllithium at −100 °C, was rapid (complete disappearance of **1b** after 5 min); however, a complex mixture of products resulted when the reaction mixture was quenched with water. Products identified were isopropyl benzoate (**3b**, 9% yield), isopropyl (*p*-bromobenzoyl)benzoate (~26% yield), and the carbinol corresponding to addition of *n*-butyllithium to isopropyl (*p*-bromobenzoyl)benzoate (~19% yield, slightly impure) together with considerable material (low R_f) assumed to be higher molecular weight condensation products. These products are analogous to, but more complex than, those reported[8] from the corresponding methyl ester of *p*-bromobenzoic acid.

The ester function in isopropyl *o*-bromobenzoate (**7**) is sufficiently hindered to permit complete halogen–metal interchange to give **8**. Studies of aliquots showed only isopropyl *o*-lithiobenzoate (**8**) after 5 min at −100 °C; the composition of aliquots taken over a 2-h period at −100 °C showed no appreciable change. When the solution containing **8** was quenched at −100 °C, shortly after its formation, with excess cyclohexanone, a mixture was obtained from which the expected lactone **9** was isolated in 43% yield; *N*-phenylphthalimide (**10**) was isolated in 53% yield when the reaction mixture



was quenched with excess phenyl isocyanate. These routes to **9** and **10** are inferior to those previously described from *o*-bromobenzoic acid[3a] or from *o*-bromobenzonitrile.[5] When the solution of **8** was warmed to −75 °C it decomposed to a complex unresolved mixture, a result in contrast to similar reactions[8] with methyl *o*-bromobenzoate which gave high yields (88%) of methyl *p*-benzoylbenzoate.

In summary, stable aryllithium reagents can be prepared and elaborated in good yields with electrophiles provided that the ester is derived from a tertiary alcohol or is otherwise sterically hindered. These procedures are not only useful for preparation of substituted benzoic esters and acids derived from them, but may offer advantages, in certain cases, to direct use of haloaryl acids, since the lithioaryl esters are generally more soluble at −100 °C than the corresponding lithioaryl carboxylates.[3a]

Experimental Section

Reaction of *tert*-Butyl *p*-Bromobenzoate (1a). General Procedure. 1-(*p*-Carbo-*tert*-butoxyphenyl)cyclohexanol (5a). *n*-Butyllithium (7.9 ml, 0.0195 mol, 2.45 *M* solution in hexane) was added, at a rate such that the temperature did not exceed −100 °C, to a cold (−100 °C, liquid nitrogen/diethyl ether bath) mixture of *tert*-butyl *p*-bromobenzoate [NMR ($CDCl_3$) δ1.56 (s, 9, CH_3), 7.45 (m, 3, ArH), 8.05 (m, 2, ArH)] (5.0 g, 0.0195 mol), tetrahydrofuran (130 ml, freshly distilled from $LiAlH_4$), and hexane (35 ml, stored over molecular sieves). The mixture was stirred for 5 min at −105 °C and cyclohexanone (2.45 g, 0.025 mol) was added at a rate such that the temperature was maintained at −98 °C. The resulting mixture was stirred for 5 min, allowed to warm to room temperature, and then poured into water (~100 ml). The aqueous layer was extracted with ether. The white solid (5.78 g, mp 91–108 °C) obtained from the dried ($MgSO_4$) ether extract was recrystallized from petroleum ether (bp 63–75 °C) to give 5.39 g (75% yield) of **5a** [mp 128–129 °C; NMR ($CDCl_3$) δ 1.60 (s, 9, CH_3), 1.45–2.00 (m, 11, aliphatic H and OH), 7.59 (d, 2, ArH), 7.98 (d, 2, ArH)].

Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.97; H, 8.71.

Other compounds shown in Scheme I were prepared similarly.

***tert*-Butyl Benzoate (3a):** 78% yield; bp 44 °C (0.03 Torr); $n^{25}D$ 1.4886 (lit.[10] $n^{25}D$ 1.4896).

Triarylcarbinol 4a. From 0.02 mol of **1a** and 1 molar equiv of *n*-BuLi, benzophenone (0.025 mol) in dry THF (30 ml) was added at −100 ° C. The crude product (9.20 g) was recrystallized from petroleum ether (bp 60–90 °C) to give a 76% yield of **4a** [mp 115–116 °C; NMR ($CDCl_3$) δ 1.60 (s, 9, CH_3), 3.25 (s, 1, OH), 7.30 (s, 10, ArH), 7.35 (d, 2, ArH), 7.92 (d, 2, ArH)].

Anal. Calcd for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71. Found: C, 80.25; H, 6.48.

***p*-Carbo-*tert*-butoxy-*N*-phenylbenzamide (6a).** From 0.02 mol of **1a** and 1 molar equiv of *n*-BuLi, phenyl isocyanate (0.02 mol) in dry THF (~15 ml) was added at −95 °C. The crude solid (6.10 g, mp

121–131 °C) was recrystallized from a mixture (80/20) of petroleum ether (bp 90–110 °C) and chloroform to give a 54% yield of **6a** [mp 147–148 °C; NMR ($CDCl_3$) δ 1.60 (s, 9, CH_3), 7.50 (m, 5, ArH), 7.90 (m, 4, ArH), 8.45 (broad s, 1, NH)].

Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.93; H, 6.52; N, 4.53.

Reactions of Isopropyl *p*-Bromobenzoate (1b). Reactions with isopropyl *p*-bromobenzoate [bp 80 °C (0.03 Torr), 86% yield from *p*-bromobenzoyl chloride and 2-propanol; composition analysis in agreement with $C_{10}H_{14}BrO_2$; NMR ($CDCl_3$) δ 1.45 (d, 6, CH_3), 5.40 (m, 1, CH), 7.50 (m, 3, ArH), 8.15 (m, 2, ArH)] were carried out as described for **1a.** Aliquots taken after 5 min showed considerable amounts of condensation products. The mixture was stirred for a total of 50 min at −105 °C and then poured into water. The organic product obtained from the dried ($MgSO_4$) ether extracts showed at least seven components by TLC. A portion (500 mg) of the product was purified by preparative TLC [silica gel, fluorescent indicator, petroleum ether (bp 30–60 °C) and ether mixture (90/10) as eluent] to give in order of decreasing R_f (1) isopropyl benzoate [9% yield; NMR ($CDCl_3$) δ 1.45 (d, 6, CH_3), 5.40 (m, 1, CH), 7.50 (m, 3, ArH), 8.15 (m, 2, ArH)]; (2) isopropyl *p*-bromobenzoylbenzoate [26% yield, mp 82–83 °C from petroleum ether (bp 60–90 °C); NMR ($CDCl_3$) δ 1.45 (d, 6, CH_3), 5.38 (m, 1, CH), 7.71 (s, 4, ArH), 7.85 (d, 2, ArH), 8.1 (d, 2, ArH) (Anal. Calcd for $C_{17}H_{15}BrO_3$: C, 58.81; H, 4.85; Br, 23.02. Found: C, 58.77; H, 4.42; Br, 23.16)]; (3) an oil, slightly impure alcohol corresponding to the product obtained by addition of *n*-butyllithium to isopropyl *p*-bromobenzoylbenzoate [19% yield; NMR ($CDCl_3$) δ 0.9 (t, 3, CH_3), 1.40 (d, ~6, CH_3), 1.40 (m, ~6, CH_2), 5.35 (m, 1, CH), 7.55 (m, 6, ArH), 8.10 (d, 2, ArH); ir (CCl_4) ν_{OH} 3440 cm^{-1}, $\nu_{C=O}$ 1710 cm^{-1}]; and (4) the major fraction, with low R_f, which was a complex mixture.

Reactions of Isopropyl *o*-Bromobenzoate (7). Isopropyl *o*-bromobenzoate [**7**, 83% yield from *o*-bromobenzoyl chloride and 2-propanol, bp 86–87 °C (0.01 Torr); NMR ($CDCl_3$) δ 1.38 (d, 6, CH_3), 5.13 (m, 1, CH), 7.43 (m, 4, ArH) (Anal. Calcd for $C_{10}H_{11}BrO_2$: C, 49.41; H, 4.56; Br, 32.87. Found: C, 49.18; H, 4.58; Br, 32.76)] was treated with *n*-BuLi as described for **1a.** Studies (NMR) of aliquots taken after 5 min showed absence of starting bromo ester and only isopropyl benzoate.

Lactone 9. To the solution prepared from bromo ester **7** (0.0206 mol) and *n*-BuLi stirred for 20 min at −105 °C was added cyclohexanone (0.03 mol) in dry THF (~25 ml) at −100 °C. The resulting solution was allowed to warm to 10 °C and was poured into dilute hydrochloric acid (~100 ml). The acidic solution was extracted with ether and the organic material obtained from the dried ($MgSO_4$) ether extracts was saponified (1.5 h) with hot 90% ethanolic KOH. The solution was cooled and extracted with ether (the ether extract contained 1.39 g of an oil which was resaponified and reprocessed to give 0.34 g, 9% yield, of lactone **9**). The alkaline mixture was made acidic (pH ~2) with concentrated hydrochloric acid and warmed at 50 °C for 5 min. The cooled solution was extracted with ether, which was subsequently washed rapidly with cold 5% aqueous NaOH. Lactone **9** (1.35 g, 34% yield, total yield 43%, mp and mmp[5] 79–80 °C) was obtained from the dried ($MgSO_4$) ether extract by recrystallization of the crude product from petroleum ether (bp 30–60 °C).

***N*-Phenylphthalimide (10).** Phenyl isocyanate (0.05 mol) in dry THF (~25 ml) was added at −98 °C to the solution prepared from isopropyl *o*-bromobenzoate (0.020 mol) 5 min after the addition of *n*-BuLi. The mixture was allowed to warm to 25 °C and was poured into water (~100 ml). Phthalimide **10** (mp 208–210 °C, from ethanol/chloroform, mmp 206–209 °C, lit.[11] mp 208 °C) was obtained in 53% yield by recrystallization of the solid mixture obtained from the dried ($MgSO_4$) organic extracts. The concentrated mother liquor contained *N,N'*-diphenylurea (mp 237–242 °C dec, lit.[12] 239 °C, separated by trituration with petroleum ether in which the urea has limited solubility) and a product assumed to be slightly impure isopropyl *N*-phenylcarbamate [mp 85–86 °C, by preparative TLC with subsequent recrystallization from petroleum ether (bp 30–60 °C); lit.[13] mp 86 °C; NMR ($CDCl_3$) δ 1.30 (d, 6, CH_3), 5.05 (m, 1, CH), 6.6 (broad s, 1, NH), 7.20 (m, 5, ArH); ir (KBr) ν_{N-H} 3300 cm^{-1}, $\nu_{C=O}$ 1710 cm^{-1}].

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.82; N, 7.82. Found: C, 67.56; H, 7.24; N, 7.82.

Registry No.—**1a,** 59247-47-1; **1b,** 59247-48-2; **3a,** 774-65-2; **4a,** 59247-49-3; **5a,** 59247-50-6; **6a,** 59247-51-7; **7,** 59247-52-8; **9,** 5651-49-0; **10,** 520-03-6; *n*-butyllithium, 109-72-8; cyclohexanone, 108-94-1; benzophenone, 119-61-9; phenyl isocyanate, 103-71-9; *p*-bromobenzoyl chloride 586-75-4; 2-propanol, 67-63-0; isopropyl benzoate, 939-48-0; *o*-bromobenzoyl chloride, 7154-66-7; isopropyl *n*-phenylcarbamate, 122-42-9; isopropyl *p*-bromobenzoylbenzoate, 59247-53-9.

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Selective Halogen–Lithium Exchange in 2,5-Dibromobenzenes and 2,5-Dibromopyridine[1]

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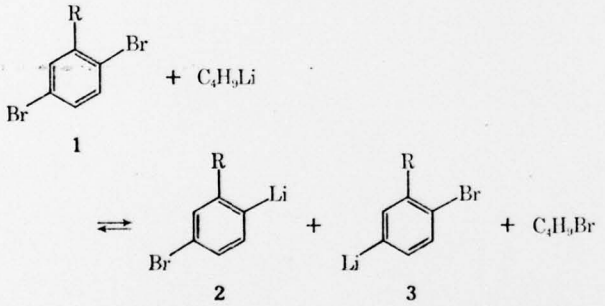
Reaction of a series of 2,5-dibromo-substituted aromatic systems with 1 equiv of *n*-butyllithium at −100 °C results in high selectivity of halogen–metal exchange when the substituent contains unshared electrons. The results suggest that product distribution at −100 °C is determined by thermodynamic rather than kinetic factors. Fair to excellent yields of derivatives of the monolithium intermediates have been obtained. Reaction of 2,5-dibromopyridine with 1 equiv of *n*-BuLi gives exclusively 2-bromo-5-lithiopyridine, which was converted in high yield into 2-bromo-5-deuteriopyridine. Reactions of 2- and 3-lithiopyridine, including their exchange with 2- and 3-bromopyridine, are described.

While selective metalation of substituted aromatic systems with alkyllithium generally occurs ortho to groups containing unshared electrons, an effect attributed to coordination of lithium with the attached functional group,[2] there has been little attention afforded[3] to selective halogen–lithium exchange in substituted dibromobenzenes (Scheme I). Extensive studies by Gilman and his co-workers[4] have established that halogen–metal exchange involves an equilibrium between reactants and products in which the lithium atom resides principally on the more electronegative carbon atom. Thus, one might anticipate that exchange in dibromobenzenes of type 1 would lead to a thermodynamically controlled mixture of 2 and 3, possibly independent of kinetic factors which might influence the proportion of 2 and 3 formed initially.

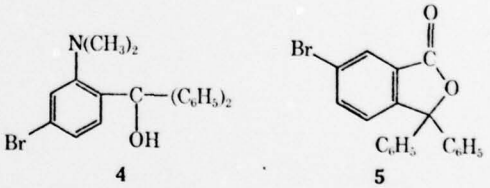
Scheme I

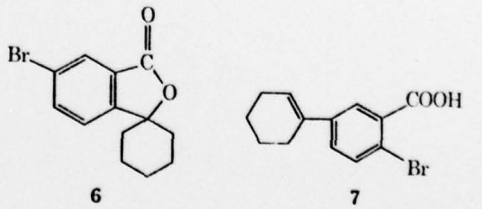


Since we were specifically interested in possible utilization of intermediates of type 2 and/or 3 for synthetic purposes, we have examined exchange in 1 with 1 equiv of *n*-C_4H_9Li in tetrahydrofuran (THF) at very low temperature (−100 °C). The course of reactions was determined by examining aliquots quenched with water, which were subsequently analyzed for starting material and the isomeric monobromobenzenes derived from 2 and 3 by GLC and/or NMR. With the exception of **1e**,[5] exchange was quite rapid and no appreciable change in ratio of products was observed after a few minutes. The results obtained are shown in Table I.

It is apparent that the product distribution shown in Table I does not correlate with Hammett σ functions (electrophilic substitution);[2b] however, with the possible exception of carboxylate,[7] the lithium atom in the product is preferentially located on the most electronegative carbon atom as judged by the inductive effect of the substituent. Whether this result is indeed a function of the inductive effect or a consequence of stabilization of the product by coordination of lithium with the substituent is not known; results with 2,5-dibromopyridine, discussed subsequently, suggest the latter and that the products are those determined by thermodynamic control.

In certain cases the aryllithium derivatives of 1 were elaborated by reaction with electrophiles. Warming the product derived from 1a effected alkylation by *n*-C_4H_9Br, formed by exchange, to give a 70% yield of 5-bromo-2-*n*-butyltoluene and 2-bromo-5-*n*-butyltoluene in the approximate ratio of 3/7. Decomposition of the product from **1c** with water gave a 70% yield (isolated) of 3-bromo-*N*,*N*-dimethylaniline; reaction of the product from **1c** with benzophenone gave carbinol **4**, isolated pure in 34% yield. Treatment of the aryllithium obtained from **1d** with benzophenone gave 5-bromo-1,1-diphenylphthalide (**5**, pure 42% yield) while reaction of the product





from **1d** with cyclohexanone gave lactone **6** and the acid **7**, isolated pure in 45 and 5% yields, respectively. The structure of **7** was assigned by comparison of its NMR spectrum with those of methyl 2-bromobenzoate and methyl 3-bromobenzoate.[8]

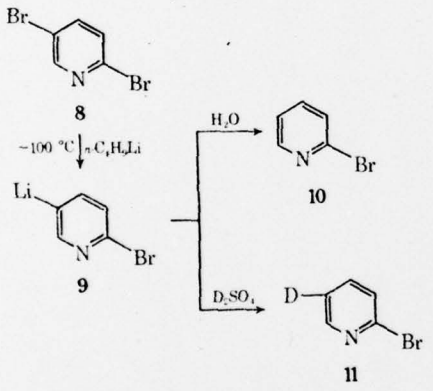
Reaction of 2,5-dibromopyridine (**8**) with 1 equiv of *n*-C_4H_9Li at −100 °C was rapid and complete and gave >99% 2-bromo-5-lithiopyridine (**9**, Scheme II). The product obtained by addition of water was essentially pure 2-bromopyridine (**10**); 3-bromopyridine was detectible (~1%) by GLC. Elaboration of **9** with D_2SO_4 gave a quantitative yield of 2-

Table I. Reactions of 1 with n-C_4H_9Li

Reactant 1	% exchange[a]	Ortho lithiation (ratio)	Meta lithiation (ratio)
1a (R = CH_3)	100	30[b]	70[b]
1b (R = NO_2)	100	100[c]	0[c]
1c [R = $N(CH_3)_2$]	100	95	5
1d (R = CO_2^-)	91[d]	90[d]	~10[d]
1e (R = NH^-)	10[e]	0[e]	100[e]

[a] Based on ratio of monobromobenzenes to 1 in aliquots as determined by GLC. [b] The ratio of monobromobenzenes was determined by NMR. The ratio of *o*-bromotoluene and *m*-bromotoluene did not change when excess dibromotoluene was added to the lithiated product. [c] Considerable by-products formed, thus it is probable that metalation also occurred at the meta position.[6] The only monobromobenzene detected, isolated (50% yield), was pure *m*-bromonitrobenzene. [d] Treatment of crude products with CH_2N_2 and analysis of esters by GLC; NMR of monobromides established nearly exclusive ortho lithiation. [e] Three equivalents of *N*-C_3H_9Li at −78 °C; products resulting from butylation by derived n-C_4H_9Br were observed and studies at higher temperature were not conducted. At −100 °C and with 3 equiv of n-C_4H_9Li no exchange was observed.

Scheme II

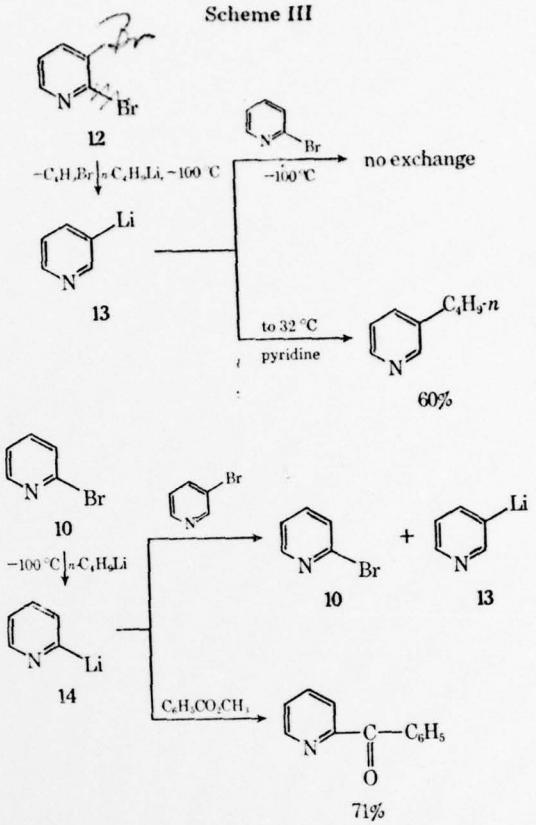


bromopyridine (11) which, by mass spectral analysis showed 85% incorporation of deuterium.

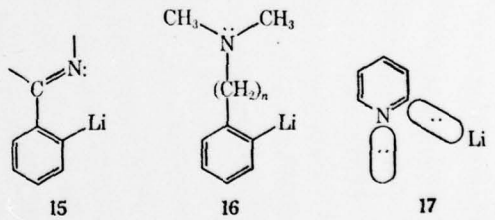
The high selectivity of lithium–halogen exchange at the 5 position of 8 was not expected since the 2 position in pyridine is more electron deficient (more electronegative) than the 5 position. Furthermore, if initial coordination of n-butyllithium with the heteroatom[2] is to play a role in determining initial exchange, then the 2 position would be favored. The above results are, however, consistent with the thermodynamic stability of the corresponding derived lithiopyridines (Scheme III). 3-Lithiopyridine (13), formed rapidly and nearly quantitatively at −100 °C from 12, does not undergo exchange[9] with 2-bromopyridine (−100 °C, 50 min); recovered 2-bromopyridine (70%) contained only a trace of 3-bromopyridine which is thought to be a consequence of incomplete initial exchange from 12. By contrast, 2-lithiopyridine (14), formed rapidly and in high yield at −100 °C from 2-bromopyridine (10), undergoes rapid exchange with 3-bromopyridine at −100 °C to give 2-bromopyridine and 3-lithiopyridine. The ratio of 2-bromopyridine and 3-bromopyridine (after water quench) was 79/21 after 20 min at −100 °C. That this ratio was not higher is thought to reflect the fact that 2-lithiopyridine is more reactive than 3-lithiopyridine and is partly consumed at −100 °C by 2-bromopyridine; consequently stoichiometry for complete exchange could not be maintained.

It is interesting to note that heteroatoms as shown in 15,[2,10] and presumably as in 16,[2] containing electrons which can be

Scheme III



orthogonal or noncoplanar to the plane containing lithium, can stabilize *o*-lithio derivatives by coordination while the heteroatom in 17, in which the unshared electrons are coplanar with lithium, destabilize the aryllithium derivative.



The above results, coupled with those summarized in Table I, suggest that thermodynamic rather than kinetic effects determine the selectivity observed in halogen–metal exchange in dibromo aromatic systems. Such reactions are of synthetic use since selectivity is generally high and fair to good yields of elaborated products are obtained.

Some attempts were made, incidental to this study, to effect condensation of lithiopyridyls 13 and 14 with 2-bromo- and 3-bromopyridine to give bipyridyls; however, such reactions gave tarry mixtures. A convenient synthesis of 3-n-butylpyridine was developed and is shown in Scheme III. Other derivatives of 13 and 14 were prepared and are described in the Experimental Section.

Experimental Section

I. Bromine–Lithium Exchange of2,5-Dibromobenzenes. A. Reaction of 2,5-Dibromotoluene (1a). General Procedure. A solution of n-butyllithium (0.02 mol, 8.65 ml of 2.3 M solution in hexane) was added to a cold (−100 °C, liquid N_2–ether) solution, under N_2, containing 2,5-dibromotoluene (5.88 g, 0.02 mol) and dry (freshly distilled from $LiAlH_4$) THF (125 ml) while maintaining the mixture at −90 to −100 °C.

Aliquots (10 ml) were quenched with 50 ml of water. The resulting mixture was extracted with ether, dried ($MgSO_4$), concentrated, and

analyzed by GLC (6 ft × 0.25 in., 20% SE-30, 150 °C, 60 ml/min He) to determine the ratio of starting material (t_R 3.75 min) to monobromotoluenes (t_R 1.62 min). The residues were then analyzed by NMR to determine the ratio of *m*-bromotoluene (δ 2.11, $ArCH_3$) to *o*-bromotoluene (δ 2.26, $ArCH_3$). The first aliquot, taken after 30 min, showed no unchanged **1a**. The ratio of *o*-bromotoluene to *m*-bromotoluene (~70/30) did not change significantly over a period of 120 min.

B. Reaction of 1-Nitro-2,5-dibromobenzene (1b). Reaction was carried out as in IA. An aliquot (10 ml) was quenched with 10% hydrochloric acid and processed as in IA. Analysis by GLC (6 ft × 0.25 in., 20% Carbowax 20M on Chromosorb W, 140 °C, 45 ml/min He) showed *m*-bromonitrobenzene (t_R 3.25 min), no *o*-bromonitrobenzene (t_R 4.75 min), and a trace of 2,5-dibromonitrobenzene (t_R 12.00 min). The entire reaction was quenched in 10% HCl and worked up as in IA. The monobromobenzenes were collected by distillation (bp 88–95 °C, 1.0 Torr). No *m*-bromonitrobenzene could be detected by NMR (aromatic, comparison with authentic samples) or by GLC. The residue from distillation was tarry and contained no *m*-bromonitrobenzene or *o*-bromonitrobenzene as indicated by GLC. The isolated yield of pure *m*-bromonitrobenzene was 50%.

C. 2,5-Dibromo-*N,N*-dimethylaniline (1c) [prepared from 2,5-dibromoaniline (0.04 mol), methyl iodide (40 g, 0.28 mol), and NaH (0.10 mol) in THF; 77% yield, bp 90 °C (0.35 Torr); NMR ($CDCl_3$) δ 2.78 (s, 6) 7.2 (m, 3)].

Anal. Calcd for $C_8H_9Br_2N$: C, 34.44; H, 3.25; N, 5.02; Br, 57.29. Found: C, 34.69; H, 3.38; N, 4.86; Br, 57.41.

2-Bromo-*N,N*-dimethylaniline [bp 40 °C (0.25 Torr), lit.[11] bp 107–108 °C (14 Torr); NMR ($CDCl_3$) δ 2.75 (s, 6), 7.00 (m, 4)] and **3-bromo-*N,N*-dimethylaniline** [bp 70 °C (0.45 Torr), lit.[12] bp 100–104 °C (2 Torr); NMR ($CDCl_3$) δ 2.75 (s, 6), 6.8 (m, 4)] were prepared by the procedure of Borsch and Hassid.[13]

Reaction of **1c** was carried out as in IA.

Aliquots were quenched with water, extracted with ether, dried ($MgSO_4$), and concentrated. The first aliquot (1 h) showed by GLC (as in IA, 190 °C) no unchanged **1c** (t_R 9.25 min), 3-bromo-*N,N*-dimethylaniline (95% by peak height, t_R 6.00 min), and 2-bromo-*N,N*-dimethylaniline (<5%, t_R 3.75 min).

D. 2,5-Dibromobenzoic acid (1d) (mp 154–155 °C, lit.[14] 153 °C, from **1a**, $KMnO_4$, and water in *tert*-butyl alcohol, 73% yield) was treated with 2 equiv of n-C_4H_9Li as in IA. **Methyl 2,5-dibromobenzoate** (mp 43–45 °C, lit. 40–41 °C[15]), **methyl 2-bromobenzoate**, and **methyl 3-bromobenzoate** were prepared from the corresponding acids with diazomethane[15] and showed retention times of 2.62, 1.5, and 1.5 min, respectively (5 ft × 0.25 in., 3% SE-30, 190 °C, 30 ml/min He).

Aliquots (10 ml) were quenched with water and the aqueous solution was extracted with ether. The aqueous solution was acidified (concentrated HCl), extracted with ether, dried ($MgSO_4$), and concentrated. The crude residual acids were treated with excess ethereal CH_2N_2; acetic acid was employed to destroy excess CH_2N_2. The ether solution was extracted with aqueous bicarbonate, dried ($MgSO_4$), and concentrated. Analysis (GLC, see above, ID) showed 91% methyl monobromobenzoates (t_R 1.5 min) and 9% methyl 2,5-dibromobenzoate (t_R 2.62 min) (after 100 min). Analysis (NMR) of the methyl monobromobenzoates (collected by GLC) showed it to be nearly pure (>90%) *m*-bromobenzoate.

E. Reaction of 2,5-dibromoaniline (1e) was carried out as IA except that 2 equiv of n-C_4H_9Li was employed.

Aliquots were quenched with water, extracted with ether, dried ($MgSO_4$), and concentrated. Analysis was made by GLC (as in IA, 180 °C, 30 ml/min He). Retention times of authentic 2,5-dibromoaniline, *o*-bromoaniline, and *m*-bromoaniline were 11.37, 3.75, and 4.75 min, respectively. Essentially no exchange occurred at −100 °C. The ratio of **1e** to *o*-bromoaniline was 95/5 after 45 min at −78 °C and 90/10 after 135 min; no *m*-bromoaniline (exchange at ortho position) was detected. NMR analysis showed some butylation at −78 °C and considerable butylation when exchange was conducted at higher temperature.

Essentially identical results were obtained when 3 equiv of n-C_4H_9Li was employed.

II. Elaboration of 1. A. 2-Bromo-5-butyltoluene and 5-Bromo-2-*n*-butyltoluene. The mixture described in IA was allowed to warm to 32 °C and maintained at this temprature for 48 h. The mixture was processed essentially as described in IA to give a mixture of 2-bromo-5-*n*-butyltoluene and 5-bromo-2-*n*-butyltoluene [70% yield, bp 78–82 °C (1.0 Torr)].

Anal. Calcd for $C_{11}H_{15}Br$: C, 58.16; H, 6.65; Br, 35.18. Found: C, 58.32; H, 6.77; Br, 34.96.

The intensity of NMR signals at δ 2.28 and 2.13 showed that the ratio of the 2-bromo to the 5-bromo isomer was ~3/7.

B. 3-Bromo-*N,N*-dimethylaniline [70% yield from **1c**, see section IB for procedure, bp 75 °C (0.6 Torr), lit.[5b] bp 259 °C (760 Torr), pure by GLC (section IB)].

C. 4-Bromo-2-(*N,N*-dimethylamino)phenyldiphenylcarbinol (4). Reaction of **1c** (0.02 mol) was carried out as in IC; the reaction mixture was stirred for 30 min at −100 ° and benzophenone (0.0203 mol) in dry THF (30 ml) was added. The mixture was allowed to warm to 32 °C, THF was removed (rotary evaporation), and ether (100 ml) and cold 10% sulfuric acid (100 ml) were added. The ether extract was dried ($MgSO_4$) and concentrated to give 6.12 g of product which was recrystallized from petroleum ether (bp 30–60 °C) to give pure **4** [2.60 g, 34% yield, mp 113–114 °C; NMR ($CDCl_3$) δ 2.41 (6 H), 7.4 (18 H), 9.5 (1 H)].

Anal. Calcd for $C_{21}H_{20}BrNO$: C, 65.97; H, 5.27; Br, 20.90; N, 3.66. Found: C, 65.76; H, 5.41; Br, 21.18; N, 3.45.

D. 5-Bromo-1,1-diphenylphthalide (5). Reaction of 2,5-dibromobenzoic acid with n-C_4H_9Li was carried out as in section ID and the mixture was treated with benzophenone as described in section IIC. The mixture obtained subsequent to removal of THF was added to ether (100 ml) and water (100 ml). The aqueous layer was separated, made acidic with concentrated HCl, and warmed for 45 min on a steam cone to effect cyclization of the intermediate hydroxy acid to **5**. The acid solution was extracted with ether which was extracted with aqueous bicarbonate to remove acids. The ether extract was dried and concentrated to give 3.33 g of yellow oil which was recrystallized from ethanol to give 1.60 g (32% yield) of pure **5**, mp 118–120 °C.

Anal. Calcd for $C_{20}H_{13}BrO_2$: C, 65.77; H, 3.59; Br, 21.88. Found: C, 65.72; H, 3.52; Br, 21.96.

Chromatography (TLC, silica gel) of the mother liquor gave an additional 12% yield of pure **5**.

E. Spiro[5-bromoisobenzofuran-1(3*H*)-cyclohexan]-3-one (6) and 2-Bromo-5-(1-cyclohexenyl)benzoic acid (7). Reaction of **1d** (0.014 mol) with 2 equiv of n-C_4H_9Li was carried out as in ID. The mixture was maintained at −100 °C for 45 min and cyclohexanone (0.0408 mol) in dry hexane (25 ml) was added. The mixture was processed essentially as described in section IID. The ether layer, obtained subsequent to treatment with hot aqueous acid, contained 1.81 g of product (mp 120–130 °C) which gave 1.73 g (45% yield) of pure **6** (mp 132–135 °C, from petroleum ether, bp 63–75 °C).

Anal. Calcd for $C_{13}H_{13}BrO_2$: C, 55.53; H, 4.66; Br, 28.42. Found: C, 55.62; H, 4.71; Br, 28.17.

Acidification of the bicarbonate solution gave 0.5 g of acid, mp 125–148 °C. Recrystallization of this product from acetone–water gave **7** [5% yield, mp 170–171 °C; NMR (Me_2SO-d_6) δ 1.6–2.5 (m, 8), 6.2 (s, 1), 7.4–7.8 (m, 4)].

Anal. Calcd for $C_{13}H_{13}BrO_2$: C, 55.53; H, 4.66; Br, 28.42. Found: C, 55.70; H, 4.73; Br, 28.15.

III. Lithium–Halogen Exchange in Bromopyridines. A. Reaction of 2,5-dibromopyridine (8, 0.01 mol) in THF (125 ml) with n-C_4H_9Li (0.011 mo) was carried out at −100 °C as described in IA.

Aliquots (10 ml, 20 and 55 min) were quenched in 50 ml of 10% HCl and the solution was extracted with ether. The acid solution was made strongly alkaline with 50% KOH and extracted with ether. The dried ($MgSO_4$) ether extract was concentrated to give residues analyzed by GLC (6 ft × 0.25 in., 20% Carbowax 20M on Chromosorb W, 120 °C, 30 ml/min He) which showed 2-bromopyridine (t_R 11.37 min, 99%) and less than 1% 3-bromopyridine (t_R 5.00 min). No 2,5-dibromopyridine (t_R 2.37 min at 200 °C) could be detected.

2-Bromo-5-deuteriopyridine. The cold solution, prepared from **8** (0.01 mol) and n-C_4H_9Li as described in IIIA, was aged for 30 min at −100 °C and then treated with 2 ml of D_2SO_4. The solution was allowed to warm to 32 °C, poured into dilute H_2SO_4 (200 ml), and extracted with ether. The acid solution was processed as in IIIA to give 1.93 g of crude amine which was analyzed by GLC (6 ft × 0.25 in., 20% Carbowax 20M on Chromosorb W, 150 °C, 30 ml/min He). Retention times of authentic samples follow: 3-bromopyridine, 1.00 min; 2-bromopyridine, 3.37 min; 3-bromopyridine (absent in the mixture) was used as internal added standard (same response as the 2 isomer). The product was essentially pure 2-bromopyridine (101% yield). Pure 2-bromopyridine was collected by GLC. Mass spectral analysis showed 85% incorporation of deuterium (by comparison of P and P − 1 peaks with undeuterated 2-bromopyridine).[16]

B. Reactions of 3-Bromopyridine (12). 1. 3-Lithiopyridine (13) was prepared from **12** (0.02 mol) and n-C_4H_9Li (0.02 mol) as described in section IA.

Aliquots (10 ml) were added to 10% HCl (100 ml) and THF was removed (rotary evaporator). The aqueous solution was extracted with ether and made strongly alkaline with 50% KOH. The solution was

extracted with ether, the dried extract was treated with ethereal HCl (100 ml), and ether was removed. The residue was treated with 15% aqueous NaOH and extracted with ether. The dried extract was concentrated and analyzed by GLC (20% Carbowax 20M, 150 °C, 30 ml/min He). Pyridine (98%, t_R 1.5 min) and 3-bromopyridine (2%, t_R 4.87 min) were detected.

2. 3-*n*-Butylpyridine. Pyridine (0.02 mol) was added at −100 °C to a solution of 3-lithiopyridine (0.02 mol), prepared as described above. The solution was allowed to warm to 32 °C, then processed essentially as described in the IIIB1 aliquot. Analysis (GLC, as shown above) showed 3-*n*-butylpyridine (t_R 2.25 min) and pyridine (t_R 1.5 min). Distillation of the crude product gave 1.62 g (60%) of pure 3-*n*-butylpyridine [bp 46–48 °C (1.5 Torr), lit.[17] bp 82–83 °C (10 Torr); NMR ($CDCl_3$) δ 0.9 (t, 3), 1.1–1.7 (m, 4), 2.5 (t, 2), 7.1–7.4 (m, 2), 8.4 (m, 2)].

3. 3-Pyridyldiphenylcarbinol. 3-Lithiopyridine (**13**, 0.022 mol) was treated at −100 °C with benzophenone (0.022 mol). The mixture was allowed to warm to 32 °C and THF was removed (rotary evaporator). Dilute H_2SO_4 (10 ml of 10%) was added and unreacted benzophenone (0.009 mol) was removed by filtration. The acid solution was made basic (KOH) and extracted with chloroform. The product (3.44 g) obtained from the dried chloroform was recrystallized from petroleum ether (bp 30–60 °C) to give 2.82 g (54% yield) of 3-pyridyldiphenylcarbinol (mp 111–114 °C, lit. 115 °C[18]).

4. Reaction of 3-Lithiopyridine (13) with 2-Bromopyridine at −100 °C. A mixture of **13** (0.02 mol), prepared as described above, and 2-bromopyridine (0.02 mol) was stirred at −100 °C for 40 min. The entire mixture was added to 10% HCl (200 ml) and processed essentially as described in IIIA aliquot. Analysis (GLC as in IIIA, 140 °C) showed the ratio of 2-bromopyridine (t_R 9.75 min) to 3-bromopyridine (t_R 6.00 min) to be 96/4. The yield of recovered 2-bromopyridine, determined by adding *o*-bromoanisole (t_R 10.75 min) and making corrections for the relative response factors of each, was 73%.

When the mixture of **13** and **10** was allowed to warm to 32 °C a black tar was obtained which was not processed.

C. Reactions of 2-Bromopyridine (10). 1. 2-Lithiopyridine (14) was prepared and analyzed as described for **13** in section IIIB. Analysis of aliquots (20 min, GLC, 130 °C) showed pyridine (t_R 2.12 min) and no unchanged 2-bromopyridine (t_R 5.62 min).

2. 2-Benzoylpyridine. A solution of **14** (0.0344 mol) was treated after 20 min with methyl benzoate (0.04 mol); the mixture was allowed to warm to room temperature, THF was removed (rotary evaporator), and the residue was partitioned between ether and water. The ether layer was distilled to give 4.46 g (71% yield) of 2-benzoylpyridine [bp 125–135 °C (0.3 Torr); picrate mp 129–130 °C, lit.[19] 124–127 °C].

3. Reaction of 2-lithiopyridine with 3-bromopyridine at −100 °C was carried out as in section IIIB4 (GLC, 6 ft × 0.25 in. 20% Carbowax 20M on Chromosorb W 30/60, 30 ml/min He). Aliquots taken at 20 and 60 min gave identical ratios of 2-bromopyridine (t_R 8.12 min) to 3-bromopyridine (t_R 4.37 min) of 79/21. Some condensation occurred as evidenced by the dark color of the crude product.

Registry No.—**1a**, 615-59-8; **1b**, 3460-18-2; **1c**, 60573-63-9; **1d**, 610-71-9; **1e**, 3638-73-1; **4**, 60573-64-0; **5**, 60573-65-1; **6**, 60573-66-2; **7**, 60573-67-3; **8**, 624-28-2; **10**, 109-04-6; **12**, 626-55-1; **13**, 60573-68-4; **14**, 17624-36-1; *n*-butyllithium, 109-72-8; 2-bromo-5-butyltoluene, 60573-69-5; 5-bromo-2-butyltoluene, 60573-70-8; benzophenone, 119-61-9; cyclohexanone, 108-94-1; 2-bromo-*N*,*N*-dimethylaniline, 698-00-0; 3-bromo-*N*,*N*-dimethylaniline, 16518-62-0; pyridine, 110-86-1; 3-*n*-butylpyridine, 539-32-2; methyl benzoate, 93-58-3; 2-benzoylpyridine, 91-02-1.

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(1) Supported by the U.S. Army Research Office through Grant DAHCO4 74 GD 128.
(2) (a) H. Gilman, *Org. React.*, **8**, 261 (1954); (b) *ibid.*, **8**, 262 (1954); (c) F. N. Jones, R. L. Vaulx, and C. R. Hauser, *J. Org. Chem.*, **28**, 3461 (1963); (d) W. H. Puterbaugh and C. R. Hauser, *ibid.*, **29**, 853 (1964); (e) D. W. Slocum and F. E. Stonemark, *ibid.*, **38**, *1677 (1973)*.
(3) The ratio of ortho–meta exchange was reported to be 22:36 by reaction of 2,5-dibromotoluene with *n*-butyllithium in ether at 32 °C: H. Gilman, W. Langham, and F. W. Moore, *J. Am. Chem. Soc.*, **62**, 2327 (1940).
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(5) Anions of atoms attached directly to the aromatic ring are known to inhibit halogen–metal exchange: (a) for CH^- cf. W. E. Parham and L. D. Jones, *J. Org. Chem.*, **41**, 1187 (1976); (b) for phenoxides, halogen exchange is generally conducted at 32 °C, cf. H. Gilman, C. E. Arntzen, and F. E. Webb, *J. Org. Chem.*, **10**, 374 (1945); (c) *p*-bromoaniline undergoes exchange at reflux in ether, cf. H. Gilman and G. C. Gainer, *J. Am. Chem. Soc.*, **69**, 1946 (1947).
(6) G. Kobrich and P. Buck, *Chem. Ber.*, **103**, 1412 (1970).
(7) Carboxylate is generally considered to have a +I effect (cf. E. S. Gould, "Mechanism and Structure in Organic Chemistry", D. C. Heath, Boston, Mass., 1959, p 207); however, δ_i is reported to be 0.05 as determined by NMR (cf. Kosower, "Physical Organic Chemistry", Wiley, New York, N.Y., 1968, p 49). The inductive effect of lithium carboxylate in THF is not known.
(8) The aromatic proton (δ 8.2) ortho to both bromine and carbonyl in methyl *m*-bromobenzoate is deshielded to a greater extent than those adjacent to only bromine or carbonyl. There is no absorption at δ 8.2 in methyl *o*-bromobenzoate.
(9) A slow reaction occurs at −100 °C, expectedly more rapid at higher temperatures to give tarry condensation products.
(10) Cf. A. I. Meyers and E. D. Mikelich, *J. Org. Chem.*, **40**, 3158 (1975).
(11) K. Auwers, *Chem. Ber.*, **40**, 2524 (1907).
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(15) W. von. E. Doering and A. A. Single, *J. Am. Chem. Soc.*, **76**, 39 (1954).
(16) We wish to acknowledge support from the Biotechnology Institute of NIH, Grant RR-220, for mass spectral analysis.
(17) E. Hardinger and E. Nikles, *Helv. Chim. Acta*, **39**, 505 (1956).
(18) H. E. French and K. Sears, *J. Am. Chem. Soc.*, **73**, 469 (1951).
(19) J. P. Wibaut, A. P. de Jonge, H. G. P. van der Voort, and P. H. L. Otto, *Recl. Trav. Chim. Pays-Bas*, **70**, 1054 (1951).

Reactions of Lithio Derivatives of Carboxylic Acids. 1. 3-Methyl-2-butenoic Acids[1]

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Received July 13, 1976

Halogen–metal exchange with 2-bromo-3-methyl-2-butenoic acid at −100 °C leads to a stable lithiovinyl intermediate which reacts with a variety of electrophiles to afford 2-alkylated derivatives in good yields. Reaction of 3-methyl-2-butenoic acid with *n*- and *tert*-butyllithium followed by protonation or alkylation is discussed.

Since 2-bromo-2-alkenoic acids are readily available from 2-alkenoic acids,[3] then possible reaction as shown in Scheme I (**1** → **2** → **3**) appeared attractive as a general method for synthesis of 2-substituted 2-alkenoic acids. The previous observation that salts of bromobenzoic acids[4a] and bromoarylalkanoic acids[4b] form stable lithium intermediates by halogen–metal exchange provided a firm precedent for this sequence; however, it remained to be established[3,5] whether proton removal from allylic (γ) positions (i.e., **1** → **6**) or lithium interchange (i.e., **2** ⇄ **4**) would impose a synthetically unacceptable limitation on such a sequence.

2-Bromo-3-methyl-2-butenoic acid (**1**)[3] was chosen as a model and halogen–metal exchange was conducted in tetrahydrofuran at −100 °C with *n*-butyllithium. The progress of

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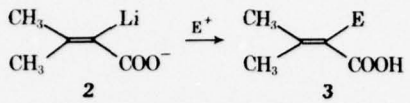
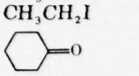
Table I. Reaction of Lithio Derivative 2 with Electrophiles (E^+)

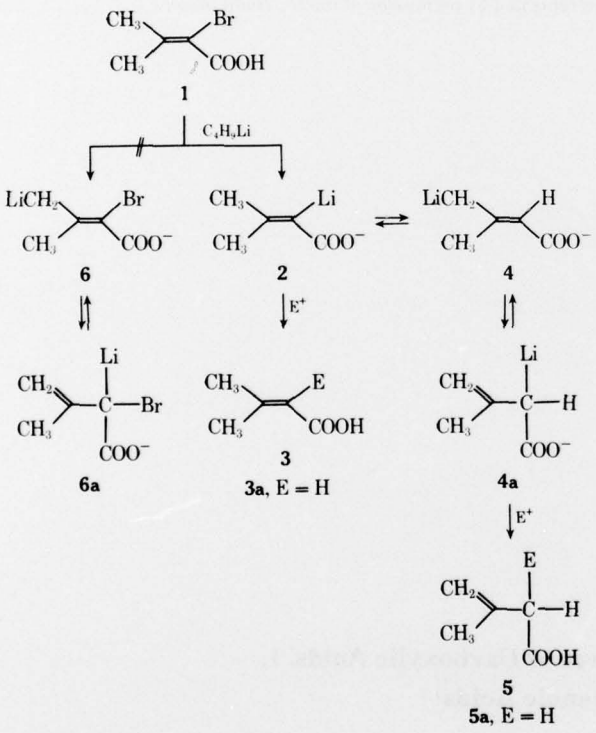


2 3

Electrophile	Product(s)	E	Isolated yield, %	Mp, °C	Ir (acid $\nu_{C=O}$), cm^{-1}
H_2O	3a, 5a	H	98[a]	45–55[b]	1695[c,d]
CH_3OD[e]	3b	D[f]	94[g]	64–66	1695[h]
CH_3CH_2I	3c	CH_2CH_3	79	42.5–44[i]	1686[c]
	3d		30	156.5–157.5 dec	1701[j]
$C_6H_5COC_6H_5$	3e	$C(OH)(C_6H_5)_2$	64	143–144 dec	1692[j]
C_6H_5NCO	3f	$CONHC_6H_5$	58	181.5–182.5 dec	1686[j]
CH_3SSCH_3	3g	SCH_3	59	80–81	1689[h]
$C_6H_5SSC_6H_5$	3h	SC_6H_5	61	85–86	1684[h]

[a] See note 5. [b] Lit.[6] mp of 3a is 69.5–70° C. [c] Melt. [d] Agrees with ref[7] value for 3a. [e] 99% D. [f] Ca. 95% D by NMR. Anal. Calcd for $C_5H_8O_2$: C, 59.98; H, 8.05. Found: C, 59.18; H, 7.99. [g] See note 8. [h] CCl_4 solution. [i] See Experimental Section. [j] KBr pellet.

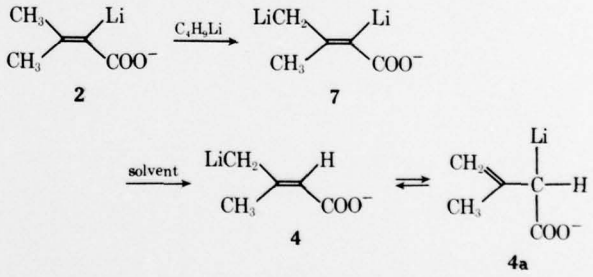
Scheme I



reaction was followed by examining aliquots which were quenched with water (identical results were obtained with saturated aqueous NH_4Cl or 10% aqueous HCl) and analyzed (by NMR) for unchanged 1 and reduced acids **3a** and/or **5a**. Halogen–metal exchange was rapid and complete when the first aliquot was taken 15 min after addition of 2 molar equiv of *n*-butyllithium per mole of acid (at −100 °C). When less than 2 molar equiv of *n*-butyllithium was employed (i.e., 1.8), the product acids (isolated in 98% yield) were 3-methyl-2-butenoic acid (**3a**) and unchanged 1 (ratio **3a**/1 = 75/25). When a 10% excess (i.e., 2.2 equiv) of *n*-butyllithium was employed, the product (isolated in 98% yield) contained mostly **3a** but was contaminated with about 10% **5a**. We were unable to eliminate either small quantities of 1 or **5a** and therefore conducted subsequent experiments with 2.0 equiv of *n*-butyllithium (ratio **3a**/**5a** = 95/5). We found no evidence (other than unchanged 1) for the formation of **6** or **6a**. The lithio derivative **2** reacted with various electrophiles (E^+) to give fair to good yields of 2-substituted 3-methyl 2-butenoic acids (**3**). The results are summarized in Table I.

The exact process by which **5** is formed remains obscure since there are a number of logical routes for its formation.[3] The fact that the ratio **3a**/**5a** does not change significantly when a solution of the lithio derivative **2** is aged at −100 or −70 °C (6 h) shows that **4** is not formed by direct conversion of **2** to **4**, or, alternatively, if there is an equilibrium between **2** and **4** it is reached rapidly and greatly favors **2**. The absence of isomer **5a**, unless a slight excess of *n*-butyllithium is employed, implicates the trianion **7** (Scheme II) as an intermediate.

Scheme II



Rapid decay of the trianion, precedented by observation with *o*- and *p*-bromophenylacetic acids,[4b] defines one reasonable path for the formation of **5a**. It is not implied that metalation occurs preferentially at either the cis or trans methyl group; however, only trans-alkylated product (**9**, Scheme III) was isolated.

A study of the reaction of 1 with *tert*-butyllithium was made in an attempt to obviate formation of *n*-butyl bromide formed during halogen–metal exchange with *n*-butyllithium. This would be advantageous since it would permit alkylation of **2** with less reactive electrophiles than were employed above. Reaction of 1 with 3 molar equiv of *tert*-butyllithium, however, led to appreciable isomerization to **5a** (ratio **3a**/**5a** = 68/32) after 15 min at −100 °C. These results are not surprising in retrospect since *tert*-butyllithium is a stronger base and possibly more prone to lead to trilithio derivatives. Alternatively, **2** could compete with *tert*-butyllithium in dehydrohalogenation of the *tert*-butyl bromide formed, thereby leading to **3a** and, subsequently, to **5a**.

Katzenellenbogen[10] prepared the lithio derivative **4** (**4a**)

Table II. Lithiation of 3-Methyl-2-butenoic Acid at −100 °C

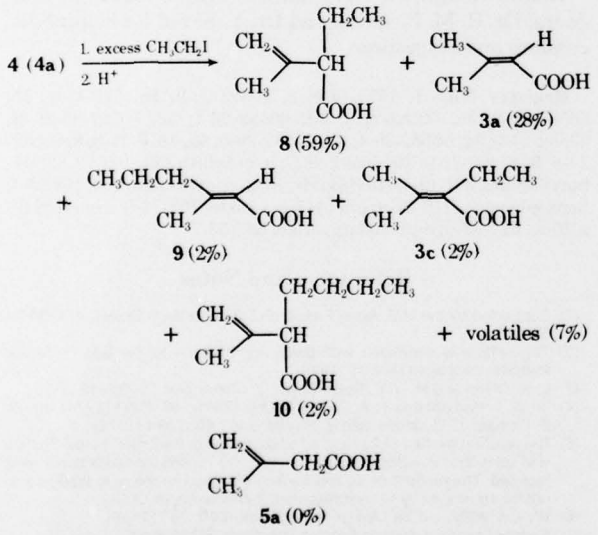
Reaction time, h	Equiv C_4H_9Li	% **5a** in product[a]	
		n-C_4H_9Li	t-C_4H_9Li
0.25	2.0	51	65
1.0	2.0	53	75
2.0	2.0	59	75
2.25	3.0[b]	63	75
3.0	3.0	71	79
4.0	3.0	73	80

[a] After quenching in water; remainder was **3a**. [b] After adding an additional 1 equiv of butyllithium in the same experiment.

by reaction of **3a** with lithium diisopropylamide (LDA) and showed that it undergoes alkylation to give almost exclusively derivatives of **5**. While one would expect **4 (4a)** to protonate in a fashion analogous to alkylation, neither this result nor the direct formation of **4 (4a)** by use of alkyllithium has been reported. The results shown in Table II show that after 1 h the product ratio is not highly time dependent and is not influenced significantly by additional alkyllithium. While these results suggest that **4 (4a)** is protonated to **3a/5a** up to the ratio 20/80, results described below for alkylation of the reaction mixture do not support such a conclusion.

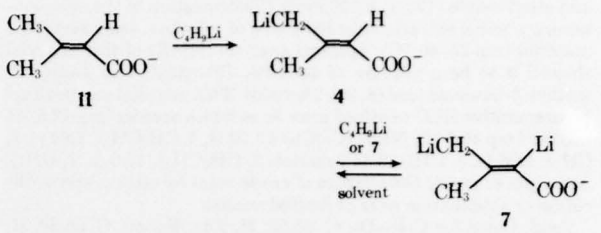
Alkylation of the lithio derivative mixture with excess ethyl iodide added 15 min after addition of 2.0 equiv of n-butyllithium (at −100 °C, see Experimental Section) afforded a mixture of acids which was analyzed by GLC[11] and NMR. The results are shown in Scheme III.

Scheme III



Compounds **3a, 3c, 8, 9,** and **10** were isolated (GLC) and characterized by NMR and combustion analysis. Formation of alkylated products **8** and **10** (evidently some n-butyl iodide was formed under the reaction conditions) corroborates Katzenellenbogen's results; only 2% of γ-alkylated product **9** was obtained. The fact that no **5a** was formed (NMR analysis of the GLC fraction containing **3a**) confirms that alkylation of **4 (4a)** was complete. Therefore it is unreasonable to conclude that the high recovery of **3a** was a consequence of incomplete alkylation of **4 (4a)** and it is strongly suggested that the unmetalated carboxylate salt of **3a** (i.e., **11**, Scheme IV) was present in the reaction mixture and, analogously, in the reaction products from the protonation experiments. Incomplete metalation of **11** suggests that metalation of **4 (4a)** to **7** is competitive with initial metalation of **11** (Scheme IV).

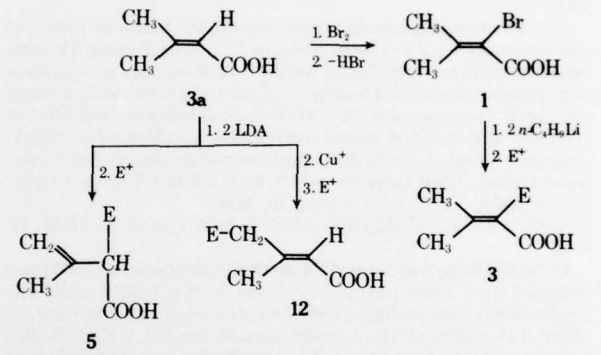
Scheme IV



Failure to isolate dialkylated products is consistent with rapid anion decay of the trianion **7** to **4 (4a)**. Such decay of trianions is precedented.[4b]

In summary, halogen–metal exchange in acids of type **1** affords reasonable yields of derived acids of type **3.** This work complements that of Katzenellenbogen and co-workers;[10] consequently it is now possible (Scheme V) to alkylate acids

Scheme V



of type **3a** either at the 2 position, as described herein to give acids of type **3,** at the 4 position through the copper dienolate[10] to give acids of type **12,** or at the 2 position to give isomerized acids of type **5.**

Experimental Section

All reactions involving organolithium reagents were conducted under an atmosphere of nitrogen. Tetrahydrofuran was distilled from lithium aluminum hydride or n-butyllithium[12] prior to use. Reaction temperatures of −100 °C were achieved with a diethyl ether–liquid *nitrogen bath. All organic residues were dried with anhydrous mag*nesium sulfate. NMR data were obtained from a JEOL Model JNM-MH-100 100-MHz spectrometer using 1–2% tetramethylsilane as an internal standard; IR data were obtained from a Perkin-Elmer *Model 137 spectrometer;* GLC *analyses were performed with a Varian* Model 910 gas chromatograph (thermal conductivity detector). Microanalyses were performed by MHW Laboratories, Garden City, Mich. All melting points were determined on a Mel-Temp heating block apparatus and are corrected.

General Procedure for Halogen–Metal Exchange. 2-Bromo-3-methyl-2-butenoic acid[3] (**1**, 4.48 g, 0.025 mol, mp 88–90 °C, lit.[3] mp 91.5 °C) and tetrahydrofuran (200 ml) were introduced, under nitrogen, into a 250-ml three-neck flask equipped with a low-temperature thermometer, pressure-equalizing addition funnel, nitrogen inlet, and mechanical stirrer. The reaction mixture was cooled to −100 °C and n-butyllithium (20 ml, 0.050 mol, 2.5 M solution in hexane) was added at a rate such that the temperature did not exceed −90 °C. Fifteen minutes after the addition of n-butyllithium was complete (examination of aliquots showed that formation of **2** was complete at this time), a solution of the electrophile in tetrahydrofuran (25 ml) was added at a rate such that the temperature did not exceed −90 °C. After an additional 15 min at about −90 °C, the reaction mixture was allowed to warm to room temperature (3 h) and poured into water (50 ml). Solvents were removed (rotary evaporation) and the mixture was extracted with two 30-ml portions of ether (to remove neutral material). The aqueous solution was cooled (0 °C) and made acidic (concentrated hydrochloric acid), and the crude product was isolated (solids by filtration; oils by extraction with five 30-ml portions of ether). The crude products were purified by either recrystallization or preparative GLC.[11]

A. 2-Ethyl-3-methyl-2-butenoic acid (3c) was obtained from **2** and ethyl iodide (19.5 g, 0.125 mol). Concentration of the acid-containing organic extracts afforded 2.60 g of colorless, semicrystalline material (mp 25–40 °C). Spectral analysis (NMR) of this material showed it to be a mixture of **3c** (97%, 79% yield) and 2-ethyl-3-methyl-3-butenoic acid (**8**, 3%, 2% yield). This material was purified by preparative GLC to afford pure **3c** as white needles [mp 42.5–44 °C, lit.[13] mp 49.5 °C; NMR ($CDCl_3$) δ 1.02 (t, 3, CH_2CH_3), 1.84 (s, 3, CH_3), 2.08 (s, 3, CH_3), 2.34 (quartet, 2, CH_2CH_3), 12.0 (s, 1, OH)]. Attempts to purify the mixture of crude acids by either recrystallization or sublimation were of limited success.

Anal. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.60; H, 9.23.

B. 2-(1-Hydroxycyclohexyl)-3-methyl-2-butenoic acid (3d) was obtained from **2** and cyclohexanone (2.45 g, 0.025 mol). The precipitate (3.83 g, mp 106–113 °C dec) obtained upon acidification of the alkaline solution was recrystallized from chloroform to afford 1.48 g (30% yield) of nearly pure **3d** as white needles, mp 135–137.5 °C dec. Two further recrystallizations afforded an analytically pure sample: mp 156.5–157.5 °C dec; NMR (acetone-d_6) δ 1.70 (s, 3, CH_3), 1.98 (s, 3, CH_3), 1.0–2.2 (m, 10, ring CH_2's), 4.2 (broad s, 2, OH's).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.69; H, 9.13.

C. 2-(Hydroxydiphenylmethyl)-3-methyl-2-butenoic acid (3e) was obtained from **2** and benzophenone (9.11 g, 0.050 mol). The precipitated crude product (6.03 g) was recrystallized from a 1:1 mixture of methylene chloride and hexane to afford 4.52 g (64% yield) of nearly pure **3e** [in two crops, mp 131–134 °C dec (sealed tube) and 121–126 °C dec (sealed tube)]. A second recrystallization afforded an analytically pure sample as finely divided white crystals: mp 143–144 °C dec (sealed tube); NMR (acetone-d_6) δ 1.46 (s, 3, CH_3), 1.88 (s, 3, CH_3), 5.30 (broad s, 2, OH's), 7.1–7.8 (m, 10, ArH).

Anal. Calcd for $C_{18}H_{18}O_3$: 76.57; H, 6.42. Found: C, 76.59; H, 6.44.

D. 2-(*N*-Phenylcarbamoyl)-3-methyl-2-butenoic acid (3f) was obtained from **2** and phenyl isocyanate (3.28 g, 0.0275 mol). The precipitated crude product (3.94 g) was recrystallized from water to afford 3.15 g (58% yield) of nearly pure **3f**, mp 174.5–176.5 °C dec (sealed tube). A second recrystallization afforded an analytically pure sample as yellowish needles: mp 181.5–182.5 °C dec (sealed tube); NMR (CF_3CO_2H) δ 2.22 (s, 3, CH_3), 2.40 (s, 3, CH_3), 7.42 (m, 5, ArH), 9.1 (broad s, 1, NH).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.76; H, 5.94; N, 6.26.

E. 2-Methylthio-3-methyl-2-butenoic acid (3g) was obtained from **2** and dimethyl disulfide (2.60 g, 0.0275 mol). Concentration of the acid-containing organic extracts afforded 3.45 g of crude product (mp 52–70 °C); this was recrystallized from hexane to afford 2.04 g (59% yield) of analytically pure **3g** [mp 80–81 °C; NMR ($CDCl_3$) δ 2.12 (s, 3, CH_3), 2.14 (s, 3, CH_3), 2.26 (s, 3, CH_3), 12.0 (s, 1, OH)] as finely divided white crystals.

Anal. Calcd for $C_6H_{10}O_2S$: C, 49.29; H, 6.89; S, 21.93. Found: C, 49.14; H, 6.84; S, 21.76.

F. 2-Phenylthio-3-methyl-2-butenoic acid (3h) was obtained from **2** and diphenyl disulfide (6.00 g, 0.0275 mol). Concentration of the acid-containing organic extracts afforded 4.46 g of crude product (mp 58–71 °C); this was recrystallized from hexane to afford 2.73 g (61% yield) of analytically pure **3h** [mp 85–86 °C; NMR ($CDCl_3$) δ 2.16 (s, 3, CH_3), 2.20 (s, 3, CH_3), 7.16 (s, 5, ArH), 12.0 (s, 1, OH)] as finely divided white crystals.

Anal. Calcd for $C_{11}H_{12}O_2S$: C, 63.43; H, 5.81; S, 15.39. Found: C, 63.60; H, 5.71; S, 15.12.

Reaction of 3-Methyl-2-butenoic Acid (3a) with Butyllithium. A. Isomerization to 5a. Reaction of **3a** (2.50 g, 0.025 mol, mp 65–67 °C, lit.[6] mp 69.5–70 °C) in dry tetrahydrofuran (200 ml) with butyllithium [initially 0.050 mol of *n*- (2.5 M solution in hexane) or *tert*- (1.6 M solution in pentane) butyllithium] was carried out analogously to the general procedure described for **1**. Aliquots were quenched in water, made acidic, extracted with ether, concentrated, and analyzed by NMR. After 2 h of reaction in the presence of 2.0 equiv of butyllithium at −100 °C, a third molar equivalent of butyllithium was added to the reaction mixture at −100 °C and additional aliquots were examined (see Table II in discussion). The product acids **3a** and **5a** could not be separated by preparative GLC.

B. Reaction of the Lithio Derivative of 3a with Ethyl Iodide. Reaction of **3a** (2.50 g, 0.025 mol) in dry tetrahydrofuran (200 ml) with *n*-butyllithium (0.050 mol) and ethyl iodide (19.5 g, 0.125 mol) was carried out analogously to the procedure described in A for the preparation of **3c**. Concentration of the acid-containing organic extracts afforded 2.47 g of yellowish liquid. Analysis of this material by preparative GLC afforded analytically pure samples of the component acids [listed in order of their elution; the composition of a volatile fraction (7%) was not determined].

3-Methyl-2-butenoic acid (3a) (28%, 28% yield) was obtained as white needles [mp and mmp 65–67 °C, lit.[6] 69.5–70 °C; NMR ($CDCl_3$) δ 2.00 (s, 3, CH_3), 2.24 (s, 3, CH_3), 5.86 (m, 1, vinyl H), 12.0 (s, 1, OH)].

2-Ethyl-3-methyl-3-butenoic acid (8) (59%, 59% yield) was obtained as a colorless liquid [NMR ($CDCl_3$) δ 0.92 (t, 3, CH_2CH_3), 1.80 (s, 3, CH_3), 1.81 (m, 2, CH_2CH_3), 3.00 (t, 1, methine H), 5.00 (m, 2, *gem*-CH_2), 12.0 (s, 1, OH)].

Anal. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.75; H, 9.61.

2-Ethyl-3-methyl-2-butenoic acid (3c) (2%, 2% yield) was obtained as white needles (mp 42.5–44 °C, lit.[13] mp 49.5 °C; NMR data are reported above).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.41; H, 9.33.

(*E*)-3-Methyl-2-hexenoic acid (9) (2%, 2% yield) was obtained as white needles [mp 33.5–36 °C; NMR ($CDCl_3$) δ 0.94 (t, 3, $CH_2CH_2CH_3$) 1.56 (sextet, 2, $CH_2CH_2CH_3$), 2.19 (t, 2, $CH_2CH_2CH_3$), 2.20 (s, 3, CH_3), 5.82 (m, 1, vinyl H), 12.0 (s, 1, OH)].

Anal. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.57; H, 9.41.

2-*n*-Butyl-3-methyl-3-butenoic acid (10) (2%, 1% yield) was obtained as a colorless liquid [NMR ($CDCl_3$) δ 0.92 (t, 3, $CH_2CH_2CH_2CH_3$), 1.2–1.5 (m, 4, $CH_2CH_2CH_2CH_3$), 1.5–2.0 (m, 2, $CH_2CH_2CH_2CH_3$), 1.84 (s, 3, CH_3), 3.10 (t, 1, methine H), 5.02 (m, 2, *gem*-CH_2), 12.0 (s, 1, OH)].

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.30; H, 10.59.

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Registry No.—**1**, 1578-14-9; **2**, 60582-20-9; **3a**, 541-47-9; **3b**, 60582-29-8; **3c**, 60582-21-0; **3d**, 60582-22-1; **3e**, 60582-23-2; **3f**, 60582-24-3; **3g**, 60582-25-4; **3h**, 60582-26-5; **5a**, 1617-31-8; **8**, 60582-27-6; **9**, 27960-21-0; **10**, 60582-28-7; *n*-butyllithium, 109-72-8; *tert*-butyllithium, 594-19-4; ethyl iodide, 75-03-6; cyclohexanone, 108-94-1; benzophenone, 119-61-9; phenyl isocyanate, 103-71-9; dimethyl disulfide, 624-92-0; diphenyl disulfide, 882-33-7.

References and Notes

(1) Supported by the U.S. Army Research Office through Grant DAHCO4 74 GD128.
(2) This article is dedicated with deep appreciation to the late Professor Parham, deceased May 21, 1976.
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(7) Sadtler Standard Infrared Grating Spectrum 677 K (melt).
(8) The reaction mixture of **2** prepared as described in the Experimental Section was quenched with excess CH_3OD (99% D); the crude product was contaminated with ~5% **3a** (deuterium content was not determined) and was purified by GLC.
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